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PRELIMINARY OBSERVATIONS ON THE TREATMENT OF POSTIRRADIATION HEMATOPOIETIC DEPRESSION IN MAN BY THE INFUSION OF STORED AUTOGENOUS BONE MARROW *

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INTRODUCTION

THE work of Lorenz et al.[1] on the protection of rodents against lethal x-radiation by the subsequent intravenous injection of bone marrow has been amply confirmed.[2] Recent studies have demonstrated that the injected bone marrow cells repopulate the depleted bone marrow of the recipient.[3, 4, 5, 6] Barnes and Loutit [7] have demonstrated that the radiation-protective bone marrow elements can be preserved for at least 83 days by freezing in glycerol and storing in the cold. These authors have further reported the treatment of murine leukemia by lethal total-body irradiation, followed by homologous bone marrow injection.[8] On the basis of these reports, Thomas et al.[9] have attempted the repopulation of human bone marrow, depressed by radiation and chemotherapy, with homologous intravenous bone marrow. In one patient these authors were able to demonstrate the presence of circulating erythrocytes of the donor type up to three weeks postinfusion of the marrow.

Thomas et al.[9] considered that the failure of homologous bone marrow to result in prolonged "takes" might be due to the fact that the x-radiation dose was not sufficiently high to produce complete bone marrow aplasia and paralysis of the immune mechanisms. Production of immune reactions to

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the infused marrow might therefore still occur. Even with successful transplants, the problems remain of late irradiation deaths from the high dosage required, or production of antibodies against the host by the homologous marrow.[10] Van Bekkum and Vos [11] have confirmed late irradiation lethality. Their results show that in mice, "homo- and hetero-transplantation is possible only after supra-lethal doses of radiation to the whole body . . . and even after supra-lethal doses . . . the immunological defense system is not fully paralyzed. . . ." (see also Makinodan [12]). Antibody production, either from the host against the graft or from the grafted tissue against the host, may be involved in the delayed mortality.[11] It appeared to us that these problems could be avoided by the use of autogenous bone marrow. This would, in general, limit the application to individuals in whom bone marrow infiltration by malignant disease had not occurred. The administration of bone marrow involved by malignant disease might also be justified, however, in order to preserve the life of an individual who had been exposed to excessive therapeutic chemotherapy or irradiation. The effect of administering autogenous leukemic marrow to a heavily irradiated patient cannot be predicted. For the present, clinical application of autogenous marrow implantation appears most promising in the cases where intensive irradiation over wide areas offers a chance for cure in otherwise fatal disease, e.g., radiosensitive tumors of the testes with metastases. Hematopoietic depression, which often prevents completion of the planned course of irradiation, may, we believe, be effectively combatted by implantation of autogenous marrow collected and preserved prior to irradiation.

Experimental Observations

For this study we have selected patients in whom irradiation was proposed for the treatment of carcinoma or lymphoma, and whose diagnostic bone marrow aspirates revealed no infiltration. Prior to the initiation of radiotherapy, bone marrow was collected from the sternum and iliac crests [13] and the marrow preserved according to the Polge method.[7] The reinfusion of the bone marrow has been accomplished three times in two patients.

Case Reports

Case 1. A 36 year old white male, one month prior to admission on September 9, 1957, had had a left orchiectomy performed because of enlargement of the testis. The pathologic diagnosis was teratocarcinoma with focal areas of seminoma. Several months previously he had had a vasectomy, at which time the left testis was said to have appeared suspect. There was moderate impairment of appetite but no significant weight loss. Physical examination demonstrated a well developed and well nourished male, 5 feet 9 inches tall and weighing 205 pounds. Genitalia revealed the left testis to be absent and the right normal to palpation. A firm, nontender nodule was present in the upper pole of the left hemiscrotum. Friedman's test was positive. Chest x-rays revealed a discrete, sharply defined, 15 mm. round density just above the right dome of the diaphragm, compatible with pulmonary metastasis.

On September 24, 1957, approximately 15 ml. of marrow were aspirated from the posterior iliac crest of the patient into a 20 ml. syringe which had been rinsed with heparin, 1,000 units per ml. Five milliliter aliquots of the marrow were placed into each of two sterile tubes containing 5 ml. of 30% glycerol in Tyrode's solution. The remaining bone marrow was utilized for cell count, desoxyribonuclease determinations and morphology. The cell count was 16,800 cells per cubic millimeter of aspirate, with normal distribution of cell types. By the Schrek eosin method,[14] 50% of the cells in the glycerol suspension were shown to be viable. The glycerol suspensions of cells were then frozen by the Polge method in a dry ice alcohol mixture, with the rate of cooling controlled in an apparatus similar to that described by Barnes and Loutit.[7] The frozen marrow was stored in a dry-ice chest.

Radiation therapy was begun on the same day (September 24, 1957), using 400 KV with 3 mm. copper filtration and a half-value layer of 4.2 mm. copper. Treatment was given in increments of about 400 r (air) per day. The left inguinal region received 2,300 r (air) or 2,100 r (tissue) through a 15 by 10 cm. port. Opposing 20 by 15 cm. umbilical and lumbar ports received 1,600 r (air) and 1,200 r (air), respectively, or 2,000 r (tissue) each.

Before proceeding further with irradiation we decided to aspirate more marrow from the sternum, since in further studies we had learned that, by using a lower concentration of heparin, greater viability of cells was possible. Into a 20 ml. syringe 1 ml. of sterile Tyrode's solution containing 100 units of heparin was introduced. From each of three sternebrae, 5 ml. of marrow were drawn into the syringe. The mixed contents were added to an equal volume of 30% glycerol in Tyrode's solution. The cell count was 24,900 cells per cubic millimeter of marrow with 83% viability by the Schrek method. The mixture was frozen by the Polge method and stored as before.

Intensive radiotherapy was then continued. Opposing 20 by 10 cm. epigastric and lower dorsal ports were given 2,000 r (air) or 2,000 r (tissue) each. Opposing 20 by 20 cm. chest ports received 1,900 r (air) or 2,100 r (tissue). A 10 by 10 cm. left subclavian port was given 2,000 r (air) or 2,000 r (tissue). An interspersed 10 by 10 right inguinal port received 2,600 r (air) or 2,300 r (tissue). Radiotherapy was completed on November 22, 1957, two months from the start of treatment. The course of therapy was somewhat more intensive than that usually given.

On November 25, 1957, the stored bone marrow was reinfused into the patient. The procedure was as follows. The ampules containing the marrow were thawed in a water bath at 37° C. With the aid of a #18 needle and syringe, the contents were transferred into a 500 ml. Fenwal plastic transfer bag. To the 40 ml. of marrow suspension in glycerol-Tyrode's solution, 20 ml. of 33⅓% glucose solution were added in accordance with the Sloviter method.[15] After two minutes of gentle mixing, 60 ml. of Tyrode's solution were added and mixed, followed in an additional two minutes by 240 ml. of Tyrode's solution. On dilution, moderate clumping of the marrow elements occurred. The estimation of viability in the diluted material was not altogether satisfactory because of the high dilution and the clumping of the leukocytes. Approximately 75% to 80% viability was estimated. With the use of a Fenwal platelet and blood recipient set, the marrow was infused through a #18 needle into an antecubital vein. By use of a donor set the plastic transfer bag was simultaneously connected to 1 L. of 5% dextrose in saline. When the plastic bag had been rinsed with this solution and the clumped marrow permitted to collect in the plastic filter, which was then squeezed repeatedly, all of the material was forced through the filter into the intravenous tubing. It was estimated that approximately 400×10^6 viable nucleated cells were administered. The infusion of bone marrow and the liter of glucose in saline was accomplished in less than two hours. The patient experienced no unusual sensation throughout the procedure and was ambula-

tory at its completion. He remained asymptomatic after the procedure until January 3, 1958, when he developed paraplegia. He was admitted for laminectomy.

The hematologic findings during and following the first course of radiotherapy are presented in figures 1 and 2. As may be seen in figure 1, radiotherapy induced an abrupt fall in lymphocytes from 2,300 per cubic millimeter to approximately 450. Simultaneously there was a progressive fall in the neutrophil count to 1,500 cells per cubic millimeter from the initial count of 6,750. The bone marrow infusion was followed by rapid recovery in both neutrophil and lymphocyte counts. Both were approximately normal four weeks following the infusion. The secondary fall in lymphocytes which occurred at the end of this observation period is probably attributable to the reëxacerbation of the malignant disease. The hematocrit and hemoglobin

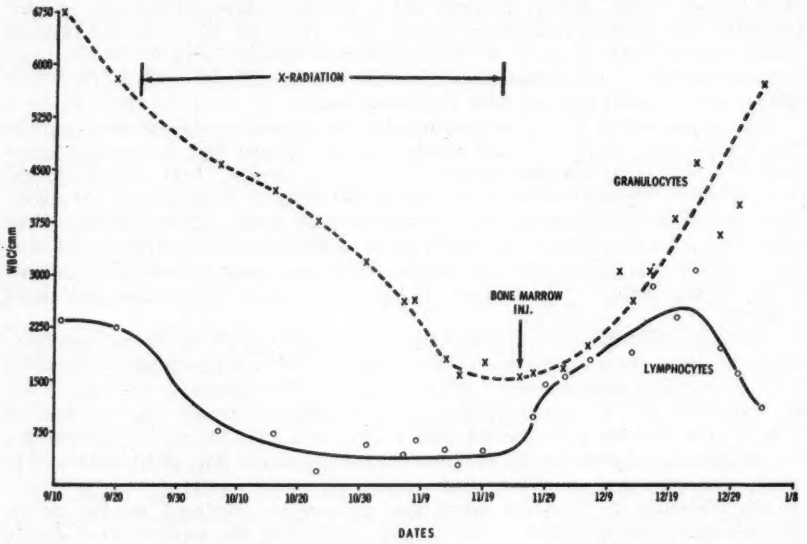

FIG. 1. *Case 1.* Lymphocyte and neutrophil response to radiotherapy and first bone marrow infusion.

(figure 2) also fell during the period of x-irradiation and recovered post bone marrow infusion. The platelet count fell sharply from the pretreatment level of 240,000 per cubic millimeter to 18,000 per cubic millimeter during the last three weeks of irradiation. It rose less rapidly than did the other elements following the bone marrow infusion, but had reached a level of 90,000/cu. mm. approximately five weeks following the bone marrow infusion. The monocyte count remained essentially unaltered throughout, while the eosinophil count showed a transitory rise to 5 to 8% (300 to 400 cells/cu. mm.) during the first three weeks of radiotherapy.

A sternal bone marrow aspiration performed on the day of bone marrow infusion revealed a very hypoplastic marrow (9,500 cells/cu. mm.). Nine days after marrow infusion (December 3, 1957), a repeat sternal bone marrow aspiration revealed a hypoplastic marrow which, however, contained numerous islands of predominantly erythropoiesis, with increased mitotic activity (figure 3). Megakaryocytes were present in less than normal numbers. The peripheral red blood cells revealed considerable anisocytosis and moderate hypochromia, with numerous poly-

chromatic erythrocytes, suggestive of two "races" of erythrocytes. Seventeen days after bone marrow infusion (December 11, 1957), a repeat bone marrow aspiration (46,200 cells/cu. mm.) showed marked progressive increase in both myeloid and erythroid activity as compared to the bone marrow examination performed eight days previously (figure 4). Bone marrow aspirated from the sternum on January 3, 1958, appeared to be normal in cellularity and morphology (figure 5).

On January 3, 1958, a laminectomy was performed and an extradural mass in the vicinity of the lower thoracic and upper lumbar vertebrae was visualized. This procedure was accompanied by transfusions, as indicated in figure 6. On January 5, 1958, 20 ml. of apparently normal marrow were collected from each posterior iliac crest into 1 ml. of Hank's solution containing 100 units of heparin. The total

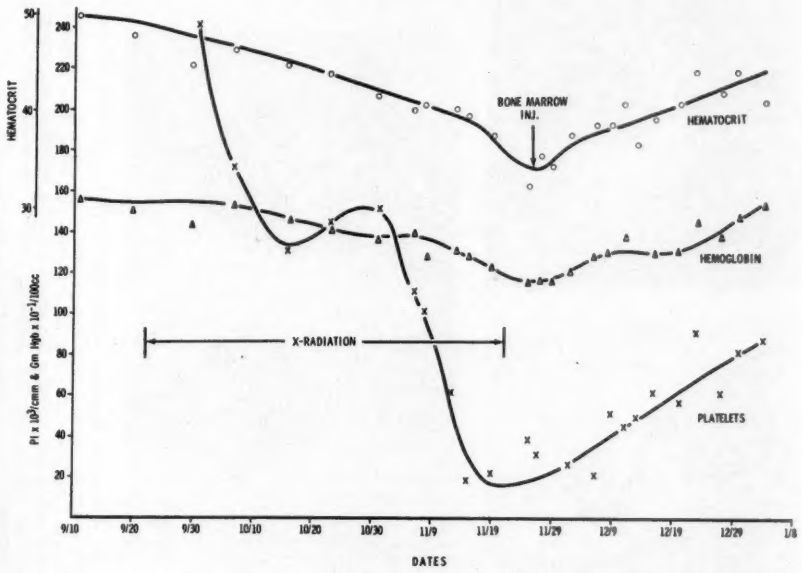

FIG. 2. *Case 1.* Hematocrit, hemoglobin and platelet response to x-irradiation and first bone marrow infusion.

number of nucleated cells obtained was 585 million, all of which appeared to be viable by the eosin stain method. The marrow was frozen and stored as before. A second course of x-ray therapy was then administered, which consisted of 900 r tissue dose to each of three oblique 10 by 20 cm. ports directed to the lumbodorsal spine, and 1,200 r to each of 10 by 20 cm. ports to the same area over a two-week period. No clinical improvement was obtained, and multiple pulmonary metastases became apparent. The second course of radiotherapy again induced a neutropenia (figure 6) which reached a nadir of approximately 1,700 neutrophils, while the lymphocyte count fell to less than 150/cu. mm. Thrombocytopenia also developed, which reached a low point of 8,000 platelets/cu. mm. At this point, manifestations of thrombocytopenic purpura were apparent in that the patient developed hematuria, cutaneous and subconjunctival hemorrhages, and bleeding from the surgical wound. On February 10, 1958, intravenous infusion of 585,000,000 nucleated bone marrow

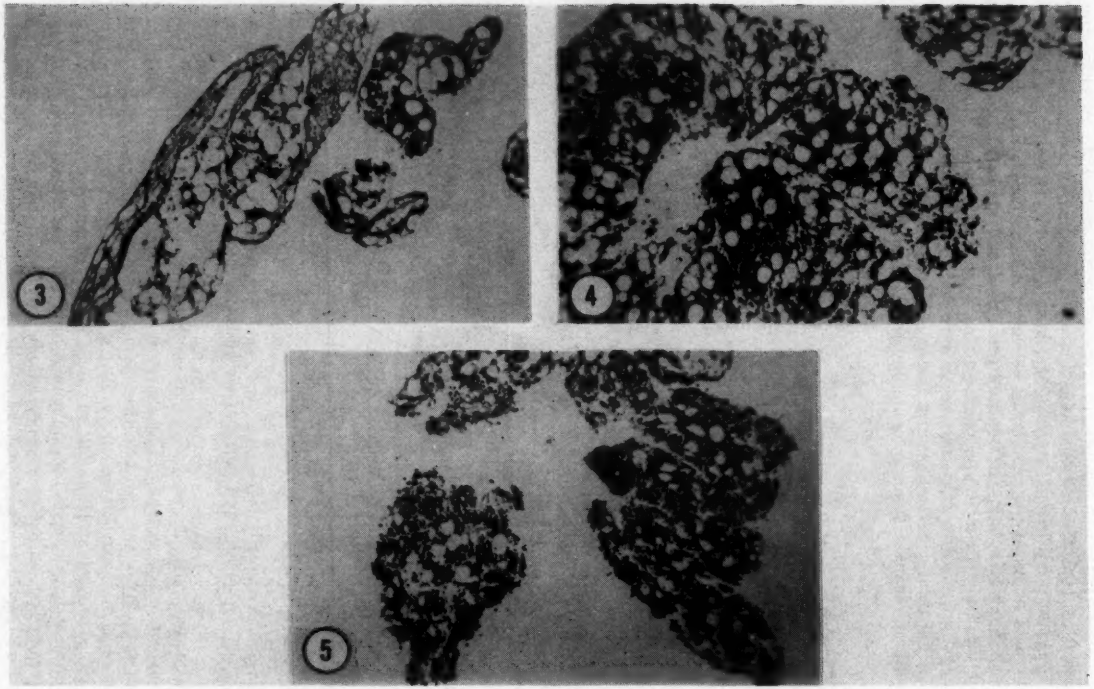

FIG. 3. *Case 1.* Section of iliac crest aspirate, December 3, 1957, one week after first bone marrow infusion. Note relatively high proportion of fat to cellular elements.

FIG. 4. *Case 1.* Aspirate from posterior iliac crest, December 11, 1957, two weeks following first bone marrow infusion. The bone marrow is still mildly hypocellular but shows reactive hematopoietic centers and erythroid hyperplasia.

FIG. 5. *Case 1.* Aspirate from sternal marrow, January 3, 1958, five weeks after the first bone marrow infusion. This is a normocellular bone marrow.

cells was performed. This was again followed by return of the neutrophils and lymphocytes to normal in from three to four weeks (figure 6). Within a week after the bone marrow infusion the platelet count had risen to 20,000/cu. mm. and the manifestations of bleeding had ceased. The platelet count continued to rise progressively to 50,000 platelets/cu. mm.

The bone marrow again showed progressive improvement from the immediate postirradiation hypoplastic fatty state (figure 7) to a normocellular marrow with moderate erythroid hyperplasia one week after bone marrow infusion (figure 8), and appeared to be hypercellular one week after that (two weeks after marrow infusion, figure 9), and was still hypercellular four weeks following the bone marrow infusion (figure 10).

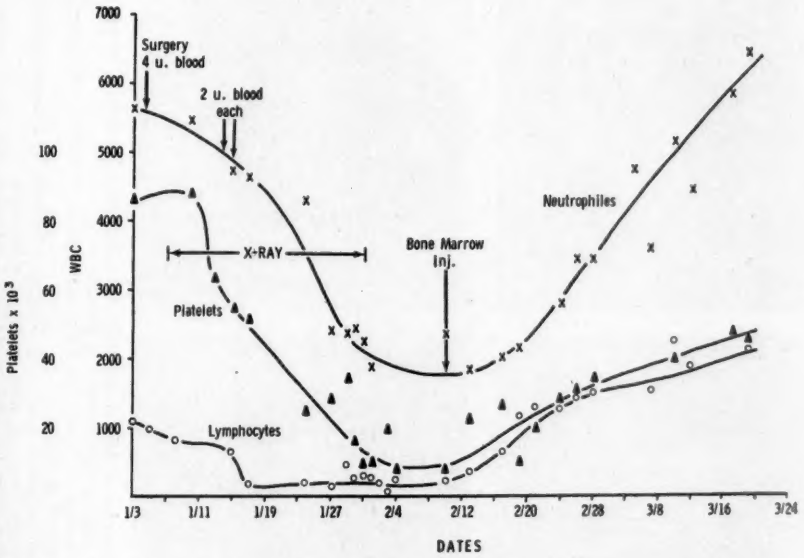

FIG. 6. *Case 1.* Response of neutrophil, platelet and lymphocyte counts to second course of radiotherapy and second bone marrow infusion.

For a period of approximately a month following the bone marrow infusion the patient appeared to be considerably improved clinically in vigor, but then began to fail rapidly, due to his metastatic disease. He died six weeks following the bone marrow infusion. At postmortem examination there was metastatic disease involving the lungs, liver, kidney and retroperitoneal nodes. Bone marrow obtained from the lumbar vertebrae was normal cytologically. The spleen weighed 275 gm. and revealed hematopoietic activity.

Case 2. The second patient was a 62 year old white male with left renal carcinoma and pulmonary metastases. The left kidney had been removed on February 3, 1958. Although his general condition was very poor, on February 19 and again on February 20, 1958, 20 ml. of marrow were aspirated from each posterior iliac crest into 1 ml. of Hank's solution containing 100 units of heparin. A total of 1.7×10^9 cells was obtained, of which 1.4×10^9 appeared to be viable by the Schrek stain. During the succeeding 10 days he received eight treatments of radiotherapy. The

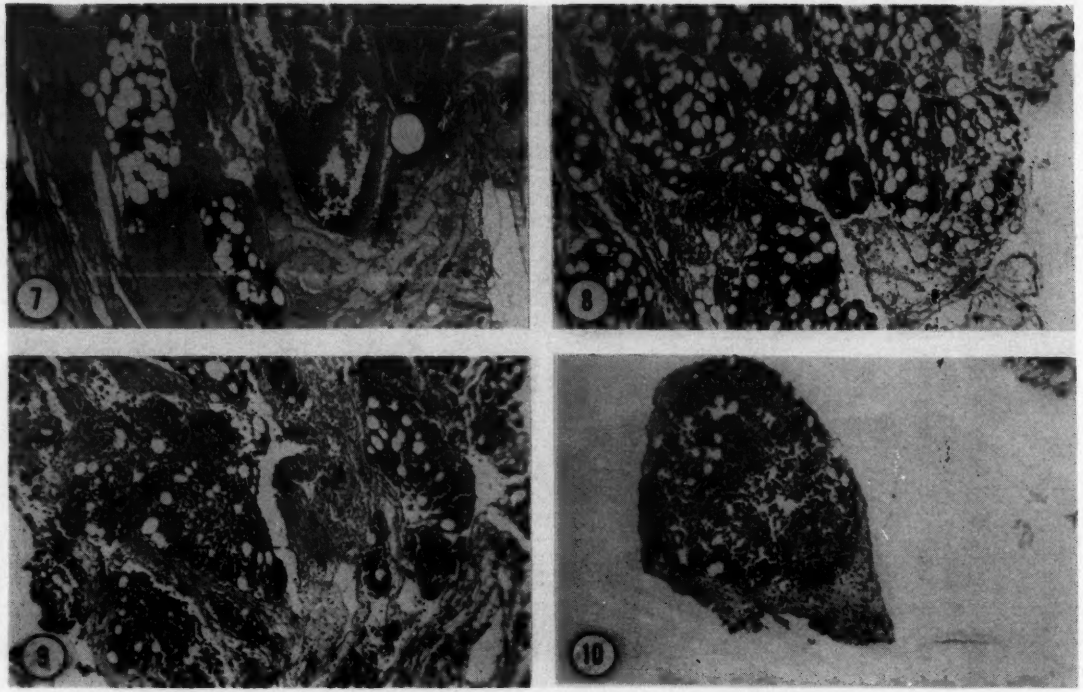

FIG. 7. *Case 1.* Iliac crest aspirate, February 10, 1958, following second course of x-ray therapy. Note again the high proportion of fat in this hypocellular postirradiation marrow.

FIG. 8. *Case 1.* Iliac crest aspirate, February 17, 1958, one week following second bone marrow infusion. This is a normocellular marrow with erythroid hyperplasia.

FIG. 9. *Case 1.* Aspirate from posterior iliac crest, February 24, 1958, two weeks following second bone marrow infusion. This is a mildly hypercellular marrow with erythroid hyperplasia.

FIG. 10. *Case 1.* Aspirate from posterior iliac crest, March 10, 1958, four weeks following second bone marrow infusion. This is a hypercellular marrow with erythroid hyperplasia.

four ports utilized consisted of one-half of the torso anteriorly and posteriorly. Each port received 200 r in air at each of two sittings. The total calculated tissue dose in the midsagittal plane was 700 r to the entire torso. The hematologic effect is shown in figure 11. On the afternoon of the last radiotherapeutic application he received intravenously the collected bone marrow, which had been diluted as described in case 1. It was estimated that 1.4×10^9 viable nucleated cells were administered. The administration was tolerated without symptoms except for slight increase in signs of congestive failure, previously noted, for which he was subsequently treated with mercurials and digitalization. Four days following the infusion of the bone marrow 2,500 c.c. of serous effusion were removed from the right thorax.

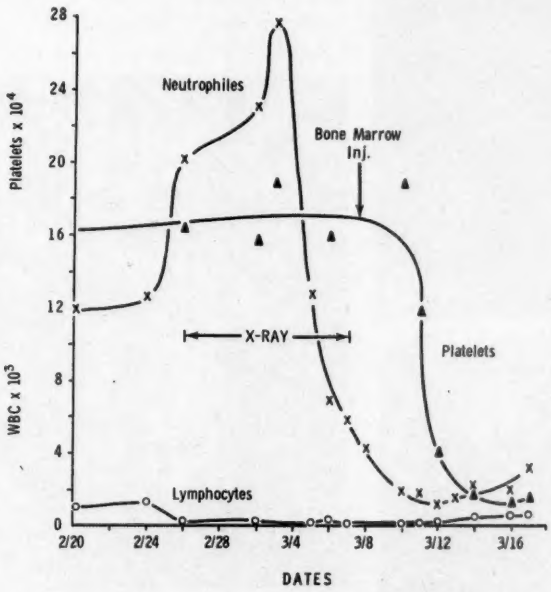

FIG. 11. *Case 2.* Response of neutrophils, platelets and lymphocytes to x-irradiation and bone marrow infusion.

The patient failed to show any clinical benefit from radiation or marrow infusion. He died on the tenth day following the bone marrow infusion. At that time (figure 11) a suggestive reversal in the fall in the neutrophil and lymphocyte counts had occurred, and the platelet count had shown no further drop during the preceding three days. At postmortem examination, widespread metastatic disease was manifest which involved the periaortic and retroperitoneal nodes, bronchial nodes, lungs, heart, testes, liver, small bowel, left psoas muscle, left diaphragm, bone marrow, pancreas and right adrenal gland. No radiation damage was observable grossly or histologically in any organ. The spleen, which weighed 250 gm., revealed moderate extramedullary hematopoiesis. The bone marrow, which had been somewhat hypoplastic before irradiation (figure 12) and had shown severe hypoplasia immediately following the radiotherapy (figure 13), appeared to be hyperplastic at postmortem examination (figure 14).

FIG. 10. *Case 1.* Aspirate from posterior iliac crest, March 10, 1958, four weeks following second bone marrow infusion. This is a hypercellular marrow with erythroid hyperplasia.

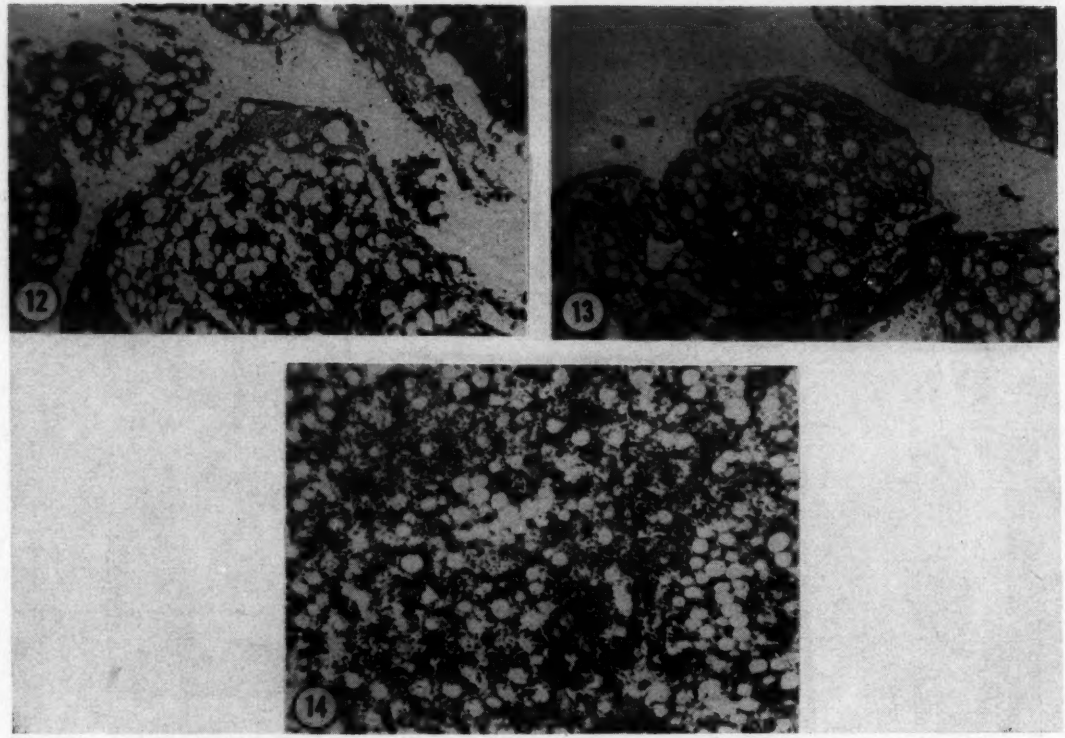

FIG. 12. *Case 2.* Aspirate from iliac crest, February 24, 1958, prior to radiotherapy. This is a moderately fatty, hypocellular marrow.

FIG. 13. *Case 2.* Aspirate from posterior iliac crest, March 8, 1958, following completion of radiotherapy. This is a markedly hypocellular marrow.

FIG. 14. Section of marrow obtained from lumbar vertebra at post mortem, March 18, 1958, 10 days following bone marrow infusion. This is a hypercellular marrow.

Discussion

Neither patient demonstrated adverse reaction to the infusion of autogenous stored bone marrow. No special precautions were taken to prevent embolization of bone marrow particles other than filtration through a plastic mesh. It was estimated that approximately 400 million viable bone marrow cells were infused intravenously on the first occasion in case 1. We were encouraged by the progressive increase in white blood cell count, hemoglobin and platelets which ensued. Rarely, spontaneous recovery at such rate may occur, although the usual response is a continued progressive fall in the formed elements of the blood for a brief period after the radiation is completed, followed by very slow recovery, in patients such as this, who received an average tissue dose of 2,000 r to the entire torso over a two-month period. The severity of the hematopoietic depression was apparent in the bone marrow aspirates and in the unusual degree of platelet depression. On the second occasion, 585 million viable nucleated cells were infused, with similar result. The second patient, moribund when the study was begun, received approximately 1.4×10^9 viable bone marrow cells intravenously following a 700 r tissue dose to the entire torso in 10 days. His survival was too brief for sufficient effect on the peripheral blood to have occurred, but bone marrow repopulation was observed.

The second procedure described for the collection and storage of the marrow yields greater than 80% viability, as measured by the Schrek stain, even after several months of storage. Collection of the marrow into 30% glycerol in Tyrode's, glycerol in saline, or Tyrode's without glycerol in the syringe, prior to addition to the 30% glycerol in Tyrode's for freezing, appears to be without influence on viability. Substitution of Hank's solution or TC199 (Difco) for Tyrode's is also without effect. Heparin concentration does appear to be important. The stock solution was Darwin Laboratories' Heparin Sodium U.S.P. 100 mg. per cubic centimeter (10,000 U.S.P. units per cubic centimeter), containing 0.45% phenol. We have found approximately 5 units of heparin per milliliter of bone marrow aspirate to be optimal (for use, the stock solution was diluted to 100 units per milliliter with Tyrode's solution), while higher concentration damages the cells. It should be mentioned that the Schrek method for determining viability is not an unequivocal measure thereof, but its convenience recommends it as a rough approximation.

The procedure described in this report is analogous to autotransplantation of skin, and should a priori be associated with no immunologic complications such as attend homologous transplants. It does not require exposing the patient to any additional risk of x-radiation beyond that indicated for the therapy of the lesion itself. It is anticipated that homotransplantation of bone marrow will succeed only following irradiation with supralethal dosages, as in animal experiments, with the risks attendant thereon.[11] It is possible that in man, as in the rat, the range of radiation

FIG. 14. Section of marrow obtained from lumbar vertebra at post mortem, March 18, 1958, 10 days following bone marrow infusion. This is a hypercellular marrow.

dosage between that which produces the required immunologic suppression for successful homologous or heterologous transplantation and that which causes death from nonhematopoietic organ damage (as intestines) is too small to permit successful transplantation.[11] Autologous transplantation may therefore prove to be the only practical procedure for the implantation of viable bone marrow elements in man. Of course, if homologous transplantation were successful, the procedure would have the advantage of being more generally applicable than the procedure of autotransplantation, which for prolonged benefit requires that the bone marrow be free from malignant infiltration. We are, however, storing marrows from leukemic patients receiving chemotherapy with the intent of preserving the patient's life from loss due to hematopoietic depression should homotransplants of normal marrow fail, even with the penalty of re-implanting the leukemic cells. The effect on the leukemic cells of re-implantation into the treated host cannot be predicted.

Because of the severe hematopoietic depression which results from rapid, intensive irradiation of the thoracolumbar region, potentially curable malignancies (particularly testicular seminomas and embryonal carcinomas, even with metastases) are often inadequately irradiated. The likelihood of salvaging such potentially curable cases would be considerably enhanced if irradiation could be pursued with less concern for the ensuing hematopoietic depression. Withdrawal of marrow prior to irradiation, with preservation and postirradiation infusion, may minimize the significance of the hematopoietic depression which often limits potentially curative irradiation.

The results reported here do not permit evaluation of the procedure of autologous marrow implantation. However, it appears to be an innocuous procedure which, if it did not cause the hematologic recovery, at least did not prevent it. It would therefore appear that the anticipatory collection, freezing and storage of bone marrow prior to irradiation (or chemotherapy) of patients with malignant disease are procedures deserving further trial. It may prove of value also for individuals in whom accidental excessive exposure may be anticipated.

This procedure is particularly applicable to those cases where there is indication for rapid administration of intensive irradiation to wide areas (with consequent radiation-induced hematopoietic depression).

Summary

Prior to the institution of radiotherapy in two patients with metastatic malignancy, bone marrow was collected and preserved by freezing by the Polge technic. The cells were stored in a dry-ice chest during the periods (14 days to two months) during which the patients received radiotherapy to the entire torso. The stored diluted bone marrows, which revealed approximately 80% of the cells to be viable, were infused intravenously

postirradiation. Serial bone marrow examinations revealed severely hypoplastic marrow at the end of radiotherapy, followed by progressive increase in active centers in both patients on the three occasions of radiotherapy and marrow infusion. Since on rare occasions spontaneous rapid recovery may occur, it cannot be concluded that the response in the hematologic picture in these patients was due to the infusion of the autogenous marrow. It can be said with certainty that the infusion of the marrow was innocuous and did not interfere with rapid bone marrow recovery, and that it may have been responsible for it.

The storage in a viable state of bone marrow permits re-infusion of autogenous marrow following radiation depression in patients who are to undergo extensive radiotherapy. No problem of immunologic reaction such as occurs with homologous transplants is concerned. The method has particular application for patients with potentially curable malignancies requiring extensive rapid x-irradiation. Such patients are often deprived of adequate therapy because of the hematopoietic depression. We are encouraged to continue the method.

Addendum

The experience reported here has been increased by two more infusions of stored autogenous bone marrow. The results show repopulation of the bone marrow within two to four weeks. A group of patients who suffered less severe bone marrow depression have been followed without reinfusion of their stored bone marrows. Serial bone marrow aspirates in these subjects revealed persistent hypoplasia two to nine months after completion of irradiation.

Acknowledgments

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Summario in Interlingua

Le technica del congelation in glycerol sub regulate conditiones de refrigeration permitte le preservation de cellulas de medulla ossee in stato viabile durante longe periodos de tempore. Nos ha utilisate iste methodo in colliger e preservar medulla ossee ab patientes destinate a reciper intense cursos de radiotherapia in le tractamento de conditiones maligne. Le theoria al base del procedura esseva que le reinfusion de tal material de character autogene resultarea in un implantation efficace, proque nulle elementos alien esserea implicate. Nostre experientias initial con iste methodo de reimplaciar medulla ossee post depression roentgeno-radiational del hematopoiese es describite in le casos de duo patientes in qui le manovra esseva effectuate tres vices. Le cellulas esseva preservate in un cassa a solidificate bioxydo de carbon durante le pericdo de inter 14 dies e duo menses quando le patientes recipeva radiotherapia del torso integre con un dosage medie al histo de 2.000 r. Le medulla, que habeva essite preservate in glycerol, esseva diluite e re-infundite per via intravenose post le completion del radiotherapia. Examines serial del medulla ossee revelava que le medulla—initialmente multo hypoplastic como resultato del depression radiational—esseva repopulate progressivemente in omne le casos. Intra duo septimanas le medulla pareva esser hyperplastic. Le experientia con patientes suffrente considerabilemente minus sever grados de depression hematopoietic per irradiation indica que un si rapide restablimento es extremente inusual. Tamen, in le tres obser-

vationes reportate il non es possibile excluder le occurrentia de restablimento spontanee, ben que un tal explication es multo improbabile. Le intervention chirurgic habeva nulle effectos adverse. Infelicemente, ambe le patientes succumbeva plus tarde a lor neoplasmas. Usque al tempore del presente reporto, duo simile experientias ha essite observate in patientes additional.

Le methodo del collection e preservation de medulla ossee ante le depression hematopoietic deberea esser applicabile primarimente in patientes con neoplasmas que es potentialmente curabile, mesmo in le presentia de metastases, si rapide e extense tractamentos radiotherapeutic es considerate como indicate. Il es etiam a supponer que le methodo pote esser applicate in patientes destinate al tractamento con agentes chimotherapeutic que es characterisate per un effecto depressori super le medulla ossee. In le caso de subjectos normal qui debe exponer se al risco de excessos de radiation accidental, le collection e preservation de medulla ossee es possibilemente de valor in un subite situation de urgentia.

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RADIATION INJURY AND MARROW REPLACEMENT: FACTORS AFFECTING SURVIVAL OF THE HOST AND THE HOMOGRAFT *

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INTRODUCTION

EXPOSURE of the entire body to ionizing radiation † in the range of 500 to 1,000 Roentgens (r) is followed by death in from seven to 14 days.[1] A failure of marrow function is the primary cause of this death, and the symptoms are primarily those of bleeding and septicemia. In a number of animal species—mice,[2] rats, rabbits,[3] dogs,[4] monkeys,[5] and chimpanzees [6]—death of this type can be avoided by the intravenous infusion of homologous marrow cells ‡ a day or two after the exposure to radiation. The infused marrow cells "home" to their appropriate sites in the marrow of the irradiated subject, divide, multiply, and thereby restore marrow function in time to save life. Preliminary clinical work on this subject in man suggests that similar phenomena apply to our species.[7, 8, 9]

Viable marrow cells may be procured in quantity from cadavers an hour or two after death,[10, 11] and may be infused intravenously into the human subject without apparent ill effect.[7] In fact, a growing body of evidence suggests that these infusions are of benefit to their recipients who, in most instances, have been individuals under treatment for blood dyscrasias. It has therefore become evident that this field of therapy, essentially that of marrow replacement, can be explored under circumstances that are beneficial to the individual studied. This primary consideration of the interest and well-being of the patient is important in American medicine, and its presence and safeguard here are most welcome.

Some patients with leukemia have received rather considerable amounts of total-body irradiation, 200 to 600 r, and an infusion of normal marrow from suitable cadavers or from volunteers.[7, 8] In some instances, remission of the leukemic process of significant duration and degree has followed these measures. In other instances the patient has experienced only temporary benefit. It would therefore appear useful to set down the guiding principles that have emerged from these meager preliminary studies in man and to relate these principles as carefully as possible to the wealth

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† Radiation that knocks electrons off molecules and produces biochemical change.

‡ Cells taken from members of the same species.

of information now becoming available from experimentation in several animal species.

Review

First, in a discussion of this type, it is apparent that therapy must be tailored to fit the individual and the disease. What is good for one leukemic patient is not necessarily good for another, and what is good for aplastic anemia may be quite another matter. Certain basic considerations, however, do pertain to all patients and may be recounted. Let us pass over for the time being the possibility that infusions of marrow are helpful in providing "building-blocks" or "regulators" for normal marrow function. Dividends of this nature attach themselves automatically to the treatments under discussion in both leukemia and aplastic anemia. Consider, rather, the problems of marrow transplantation on their immunologic bases, the problems of what the host does to cells infused from a foreign individual, and what these cells in turn may do to their new host.[8] Here is the familiar ground of homograft immunology, the immunology controlling transplantation of cells from one individual to another.[12]

In this exciting realm of "spare parts" [13] we have two newly recognized, basic biologic phenomena with which to help ourselves. It is the recognition of these phenomena that has infused life into this ancient and wistful field. First is Billingham's principle of "actively acquired tolerance," a phenomenon in many respects the opposite of immunity.[14] Second is the discovery of radiation chimeras,[15] * in some respects the biologic counterpart of the transmutation of elements and our chief biologic inheritance from a troublesome atomic era.[16] Let us develop this notion of "tolerance."

An individual is tolerant of himself; he will take grafts from himself—autografts—but will not take grafts from others—homografts. His defense system, his lymphoid immunologic mechanism, when mature, distinguishes his tissue from that of outsiders. Some marker denoting "self" is on his molecules and not present, or different, on the molecules of others.[17] His mature lymphoid tissue has come to recognize this difference and to react to it. There is a time, however, in early neonatal or fetal development, when the pattern of immune responses is not yet established and when the ability to recognize these markers and to distinguish "self" from "nonself" is not yet present. At this time of immaturity and ductility it is possible to induce a change in the usual pattern of reaction, to induce tolerance and so to prepare for subsequent successful homografts.[14]

Nature demonstrates this repeatedly in cattle.[18] In cattle, vascular anastomoses exist between the placentas of twin calves even when the twins are not identical and originate from separate ova. This communication permits exchange of cells in circulation, notably primitive blood cell pre-

* A chimera is an animal bearing cells of different genotype, cells of different hereditary chromosomal origin, as, for example, a homograft of marrow following lethal irradiation.

cursors—marrow, that is—at an early stage in development, at a time before "self" is recognized. In consequence, a condition of mutual tolerance of these cells emerges. The twin calves share the primitive marrow cells, share blood groups, and can be shown to exchange skin grafts or kidneys [19] or what you will in later life, though being of diverse heredity and distinctly not identical individuals.

Thus tolerance extends beyond permanent growth of the tissue used to induce tolerance, and embraces future acceptance of other tissues of the same donor. The reason for this is that the important antigens of homograft immunity are constituents common to all cells of a given individual and presumably are a direct reflection of his genetic chromosomal consti-

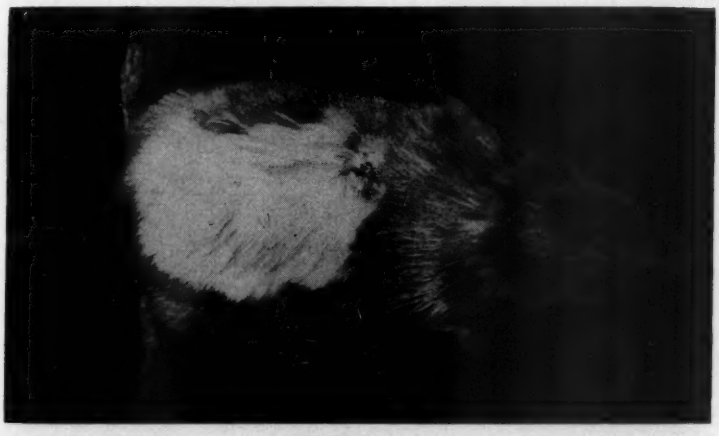

FIG. 1. DBA/2JN mouse with BALB/cAnN skin graft after administration of high dosage x-radiation (800 r) and BALB/cAnN X DBA/2JN, F_1 bone marrow. The photograph was taken 150 days after skin grafting. (From: Main, J., and Prehn, R.: Successful skin homograft after the administration of high dosage x-radiation and homologous bone marrow, J. Nat. Cancer Inst. **15**: 1023 (Feb.) 1955.)

tution.[20] This fortunate universality of determinant antigens allows successful transplantation of other organs once tolerance to a single tissue (in this case, bone marrow) has been established.

In some species, tolerance can be induced by injecting the newborn animal with a few marrow cells from a prospective donor. For example, artificial reproduction of nature's own experiment as described in cattle is not difficult in the rodent because the pattern of immune resistance, the pattern of self-recognition, is not rigidly fixed during the first neonatal day. Tolerance on this day is easily induced by a simple intravenous injection of a few marrow cells from a prospective donor. It cannot be easily induced on the next day. Animals so prepared readily accept homografts of skin or other tissue in later life, but only from the donor to whom they were conditioned in neonatal life. Tolerance actively acquired to essential cell

antigens during a ductile state in early neonatal development is like immunity, a relatively permanent acquisition. We expect to make use of corollaries of these embryologic phenomena later in the discussion of satisfactory radiation chimeras.

Let us turn now to lethal irradiation and marrow transplantation. Here is a mouse (figure 1), from the work of Main and Prehn.[21] He is a brown mouse. He has a skin graft from a white mouse. As an adult, without neonatal preparation, this brown mouse received a lethal irradiation of his entire body with a dose of about 800 r. The irradiation stopped mitosis in erythropoietic tissue, in myelopoietic tissue and in lymphopoietic tissue. If let alone, the mouse would have died in from seven to 14 days of a deficiency of the formed elements of blood, no platelets, no leukocytes, no

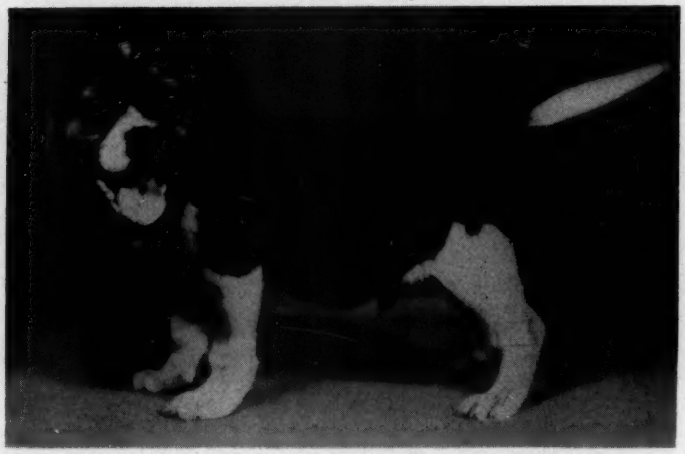

FIG. 2. A young beagle five weeks after 800 r of total-body irradiation and a marrow transplant from a sister.

lymphopoiesis, no immune defense, no new antibody formation. Death would have been from bleeding and from septicemia. But since the dose of irradiation given was sufficiently uniform and intense to destroy all mature lymphoid tissue and, with it, all patterns and means of immunologic defense, the brown mouse gratefully accepted and tolerated an intravenous infusion of foreign marrow cells from a white mouse. These members of the foreign erythropoietic, myelopoietic and, to a certain extent, lymphopoietic systems "homed" to their appropriate sites in the bone marrow, spleen and lymph nodes,[22] multiplied there, and formed active bone marrow and more or less active lymphoid organs in time to save the life of the brown mouse. In a sense, the irradiated and marrow-transplanted animal was taken over by a new defense system derived from the white mouse. The lymph nodes and spleen, as well as bone marrow, are now populated by cells

of the white mouse. The pattern of immunologic reaction therefore honors the password or marker of cells of the white strain. This is not surprising, since the new defense system, such as it is, is now composed of cells of the white strain. The brown mouse will therefore accept and tolerate skin (and other tissue) from the white mouse, as the figure showing the skin graft indicates.

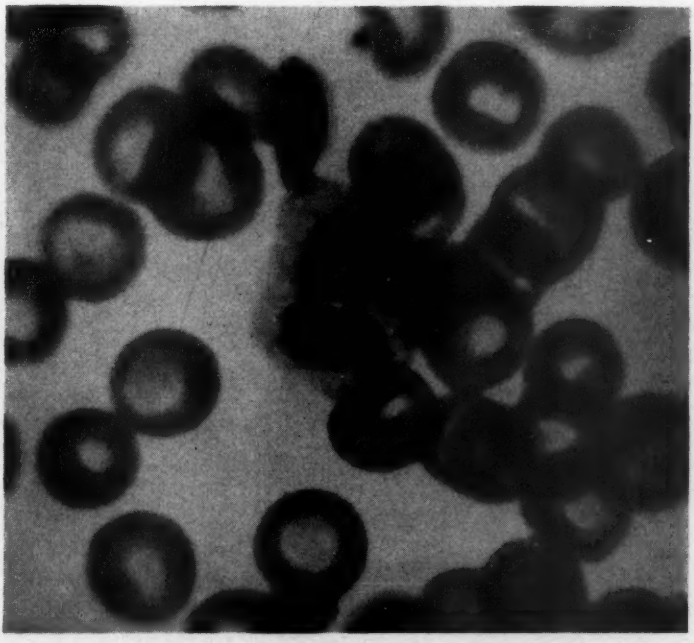

FIG. 3. A polymorphonuclear leukocyte from the peripheral blood of the male dog shown in figure 2. The small blob of nuclear material, almost completely segmented from the rest of the nucleus, indicates that this leukocyte is of female origin.

These, then, are the broad outlines of the radiologic approach to successful homotransplantation: lethal irradiation, life-saving marrow transplantation, and then homografts as desired from the marrow donor.

Now let us look at some of the details and problems. In the first place, you will have noticed that marrow is not in most species a good source of cells with which to repopulate lymph nodes and spleens that have been depopulated by radiation. Marrow is primarily erythropoietic and myelopoietic rather than lymphopoietic. The lymph nodes and spleens of irradiated animals saved from death by marrow transplantations are but partly restored to normal. These animals remain immunologic cripples, prone to death from intercurrent infection.

The young male beagle shown in figure 2 was exposed to 800 r of total-body irradiation. His own marrow and lymphopoietic systems were effectively destroyed. Death was avoided by an intravenous infusion of several billion marrow cells from a sister on the third day after his lethal exposure to irradiation.[23] He looked very fit when photographed eight weeks later, and in fact was at no time significantly ill. But this animal, though he looks well, is an immunologic cripple. Unless isolated in healthful surroundings, watched and carefully treated with antibiotics he will pick up a chronic bronchial infection and die in from three to four months from

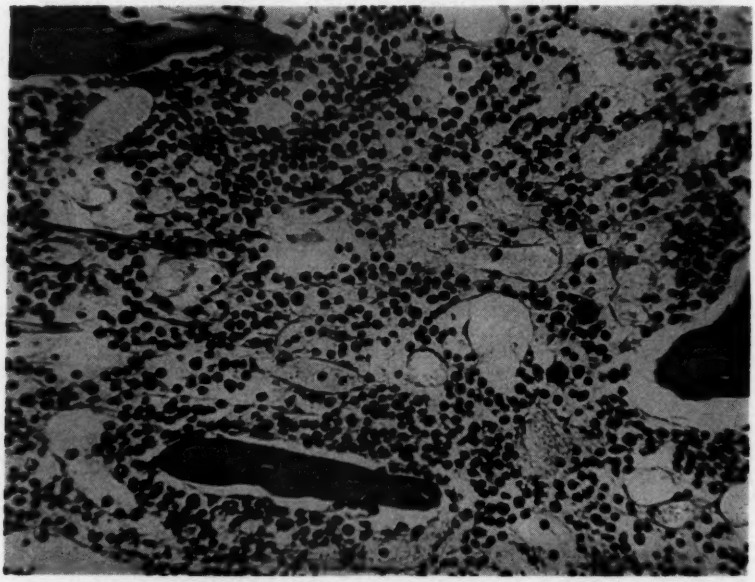

FIG. 4. A section of normal bone marrow from autopsy of the dog shown in figure 2. There is moderate myeloid hyperplasia associated with his terminal infection.

chronic pulmonary disease, weight loss and terminal pneumonia. Clinically he is like an agammaglobulinemic or dysgammaglobulinemic patient. There is something wrong or deficient with his lymphoid defenses.

The marrow transplant, on the other hand, is functioning well. It really belongs to the dog's sister, as shown by the fact that the polymorphonuclear leukocytes in circulation now have the familiar sex chromatin marker of the female [24] (figure 3). Figure 4 shows the marrow. It is normal. Myelopoiesis is perhaps overactive. The peripheral white blood count is elevated to 30,000 or 40,000, as the animal tries with leukocytes seemingly to compensate for his lack of production of circulating antibody. His lymph nodes (figure 5) show his deficiency. Lymphoid follicles are rarely found, the architecture of the node is not restored to normal, and the normal

lymphoid hyperplasia expected in the presence of infection is absent. Congdon, Makinodan and their colleagues at Oak Ridge, working with mice, have similar studies,[25, 26] and have documented the fact that such animals fail to show a normal antibody response to the administration of foreign antigens.[27] They are indeed immunologically deficient, and must be watched and taken care of or intercurrent infection will kill them just as it does the agammaglobulinemic child.

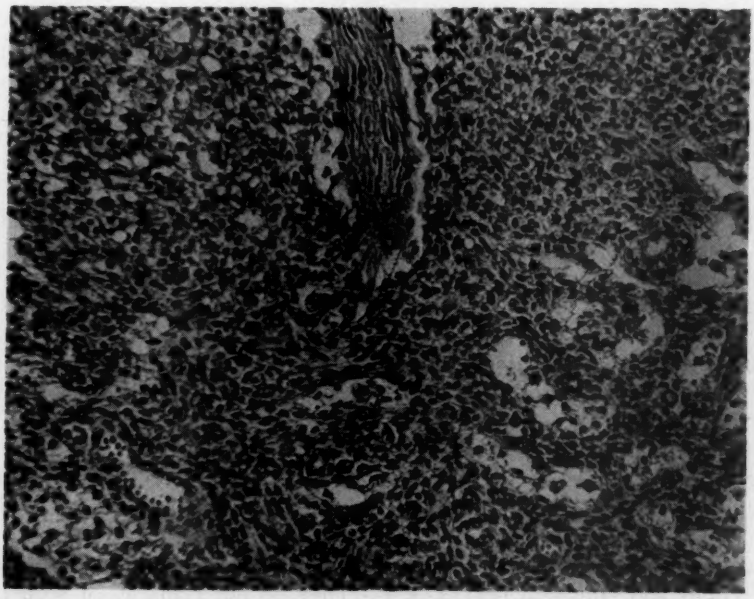

FIG. 5. Section of a lymph node from autopsy of the dog shown in figure 2. The lymph node is not normal. The usual architecture is not present. The node is relatively acellular, and germinal follicles are absent.

Since marrow is not a good source of the cells needed to repopulate lymph nodes and lymphoid follicles after their destruction by lethal irradiation, something more than marrow needs to be used in the treatment of the lethal radiation casualty or in the treatment of the lethally irradiated leukemic patient receiving marrow transfusion.

Adult spleen or lymph node tissue may not be added to marrow infusions as a remedy for the needs of lymphoid replacement because these adult lymphoid cells have a mature pattern of immune reaction and are not tolerant of the defenseless irradiated host.[28] They react against host tissue antigens and, when administered in more than the minimal number usual in adult marrow, tend more to destroy than to repopulate the lymph nodes and splenic follicles in which they lodge. Thus too many of them make matters

worse rather than better. The obvious remedy is fetal tissue, either totipotential or specifically lymphoid. The argument runs as follows [13]:

The host, if well irradiated, is defenseless. His lymphoid mechanisms and patterns of resistance are gone. Transplants of marrow will keep him alive. He cannot fight grafts of marrow or of any other tissue, any more than he can fight bacteria. If his lymphoid areas are repopulated by intravenous infusion of fetal lymphoid cells, these cells, if sufficiently immature, will acquire tolerance to the tissue antigens of their new homes, as was described earlier in the embryologic portion of this discussion. A satisfactory and peaceable restoration of lymph nodes and splenic follicles will ensue.[29]

Let us now turn to the treatment of man. The first question to be answered is, Who is going to be treated, and for what? We do not have many acute radiation casualties. Accidents with bombs or with reactors have exposed no one to lethal total-body irradiation. A few laboratory accidents have occurred and have been reported.[1] We do have a number of patients with diffuse neoplasia, such as leukemia, who die when conventional chemotherapy fails, and we do have a number of patients with renal disease who die in uremia. Should an effort be made to irradiate these individuals, when other treatment has failed, to provide them with transplants of normal marrow or a new kidney? [13] It would seem that such patients have little to lose and much to gain, and that their physicians must decide these matters.

There is evidence that delayed effects of irradiation per se will not be particularly troublesome in patients receiving 800 to 1000 r distributed evenly through the entire body. Mice that, through marrow replacement, survive the acute hazards of irradiation in this range have essentially normal life spans, provided they are successful in avoiding late deaths from infections and lymphoid deficiencies.[2] They do not come down with leukemias or radiation-induced neoplasias in significant numbers. Dogs have survived that have been exposed to 600 r of total body irradiation and then given a bit of their own marrow that previously had been removed and set aside for this purpose.[30] At the end of two years they show no lack of well-being.[31] This latter is a pertinent and helpful observation of the relatively benign late effects of radiation in situations such as those we are now discussing.

We have irradiated some leukemic patients.[7, 8] Others have done the same,[9] and we and others have tried marrow transplantations in these patients and in similar patients receiving marrow-toxic doses of chemotherapy. At least one patient in Boston with uremia has been irradiated and given marrow and had a kidney transplanted.[32] The field is moving along.

Marrow-toxic drugs such as nitrogen mustard seem a little difficult to control in the super-usual dosage required for an effect upon transplantation

immunity.[38] Moreover, these drug effects, though real, are at present less well described than is the case with irradiation.[7] It may be sufficient, therefore, to mention that chemotherapy is an approach of promise in the field of transplantation, and that some patients with neoplasia appear to have benefited from marrow infusions following exceptional doses of chemotherapeutic agents.

To return to irradiation, let us review the procurement of bone marrow, the methods for handling it and some of its uses. The supply of fetal hematopoietic tissue is limited.[7] One good specimen a week has been a fair metropolitan average for us. From the livers or bones, depending upon the age of gestation, we obtain one or two billion nucleated fetal hematopoietic cells, and from the spleen a smaller number, predominantly lymphoid. We do not know the age of gestation in man at which these lymphoid members are still sufficiently immature to be capable of acquiring tolerance to the adult host into whom we inject them, and this is an important point to settle at the earliest opportunity.

Injections of fetal hematopoietic material appear innocuous as far as immediate effect is concerned. Our first patient, two years ago, received fetal marrow from a fetus of 28 weeks,[7] and our last patient, several weeks ago, received fetal hematopoietic tissue from the liver and spleen of a fetus of 16 weeks.[8] The material to be injected was broken into a suspension of single cells by repeated passage through a series of fine screens, the last having a porosity of 43 μ.[34] The suspending fluid was a tissue culture medium with a little added human albumin or serum, type AB.

A similar screening procedure is followed in preparing adult marrow for injection.[7, 11] In no instance has an untoward event occurred. Cells from cadavers, both fresh cells and cells frozen in glycerol,[10] marrow cells from aspiration biopsy of the ilium or from bone removed at surgery,[7] all have been infused repeatedly in a dozen patients without sign, symptom or histologic evidence of embolic phenomenon. Colleagues elsewhere, with less rigorous screening procedures, seem also to have had no trouble infusing marrow suspensions intravenously in a variety of patients.

We have killed several dogs promptly while trying to infuse suspensions of splenic cells, both fetal and adult, and we are impressed by the necessity for screening and for carefully washing suspensions of spleen that are to be used intravenously.

From adult cadavers we, or our associate, Dr. Leonard Atkins, at the marrow bank in Boston, obtain 10 to 60 billion nucleated marrow cells from anterior vertebral bodies exposed by sterile laparotomy and evisceration.[11] These cells are alive if taken within an hour or two of the patient's death.[10] They synthesize nuclear material, they divide, they can be frozen and stored at $-80°$ C. in glycerol,[10] and, as in the case of animal marrows,[10, 35] when infused intravenously into an appropriately irradiated subject they repopulate his marrow spaces.[7]

The optimal number to be infused is not known. Probably the more cells the better, and the sooner thereby the reëstablishment of marrow function. Such is the case in animals.[36] Twenty-five billion seems a good round number, and we know of one patient who has received 100 billion.

Marrow is usually infused the day following irradiation. Figure 6 shows the total red cell population (top line) of a leukemic patient given stored cadaver marrow after moderate total body irradiation a year or so ago.[7]

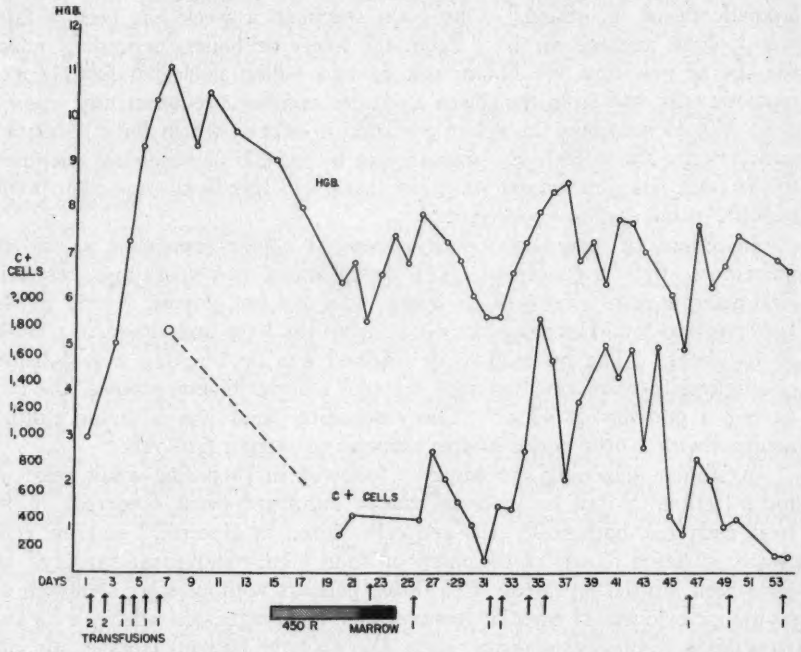

FIG. 6. (Reproduced by permission from Thomas, E. D., Lochte, H. L., Jr., Lu, W. C., and Ferrebee, J. W.: Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy, New England J. Med. 257: 491, 1957.) C + cells are plotted in thousands per cubic millimeter. It may be seen that from the thirty-fifth to the forty-third day more than half the circulating erythrocytes were C +.

The bottom line shows the red cell population attributable to the marrow graft. In the Rh blood groups the patient was C negative, the marrow graft was C positive. Two or three weeks after the infusion of marrow most of the patient's cells were agglutinable by anti-C serum. At this stage, presumably, on the basis of what is known to happen in animals and on the basis of the above specific evidence, the patient was living on his C-positive marrow graft. The patient had not received more than 300 r. It was therefore expected that the graft would be temporary but that his own marrow would regenerate. He lost his graft but marrow function

returned and he went home. He remained immunologically inadequate and died eight months later, not of leukemia, but of a yeast infection of his sphenoidal sinus.[8] In this individual a temporary marrow transplant probably helped at a critical period of marrow insufficiency that immediately followed irradiation.

We have worked with a dozen patients,[7, 8] all terminal, all desperately ill, all poor risks by any clinical criterion. Most had leukemia. No one of them has been irradiated in a satisfactory manner, and we know of no patient anywhere who has been. It is impossible, therefore, from our experience or from the work of others, to draw final conclusions as to the clinical usefulness of the radiologic approach to homotransplantation in man. Certain problems can be discussed. The basic immunology and the procurement of marrow and its administration have been outlined and are not unfamiliar. The problem of infection, both acute and chronic, in the defenseless irradiated host, particularly in the leukemic patient, is a problem readily understood by clinicians. It is a difficult problem—most of our patients die of sepsis.[8] The question of how much irradiation to give and how to give it is undetermined. The answer can only be inferred from such considerations as the following.

One probable reason why marrow transplantation and suppression of leukemia [37, 38] have shown promise in the mouse is that this animal is not large. It is easy to get uniform radiation effects that catch most of the leukemic cells and depress most of the immune mechanisms in these small creatures using ordinary radiation equipment. It should not be expected that similar results will be obtained in man without the use of extra-large beams and powerful rays consistent with his greater size and thickness.

Dosage rate is important. A low dosage rate is better for the patient. Too many cells breaking up too quickly make him ill. High voltage, diffuse radiation administered for a period of from five to 20 hours to a critically ill patient requires physical arrangements not usually available. Figure 7 shows an arrangement that seems feasible. The patient lies on a centrally placed bed between two cobalt-60 units having a photon energy equivalent to the mean output of a 3 million volt x-ray apparatus. The rays cover him from head to foot and from both sides, and give a continuous, diffuse, uniform radiation effect through the entire body.[39, 40] Treatment may be continuous or interrupted over a period of from one to three days. This is comparable to what works in the mouse. It has not yet been applied to man. When it is applied, the question of total dosage as well as the rate of dosage will be important.

In the rodent with too little irradiation, the marrow graft is temporary but the host marrow regenerates. We have seen this happen in man. With adequate radiation the graft is permanent and the host marrow does not regenerate. In between—somewhere around 500 r in the rodent—neither host marrow nor graft marrow succeeds adequately, and when this happens

mortality is high.[41] We may have seen this in some of our patients. The in-between dosage to be avoided in man also may be around 500 r but neither its position nor its degree of importance is defined. Progress is understandably slow.

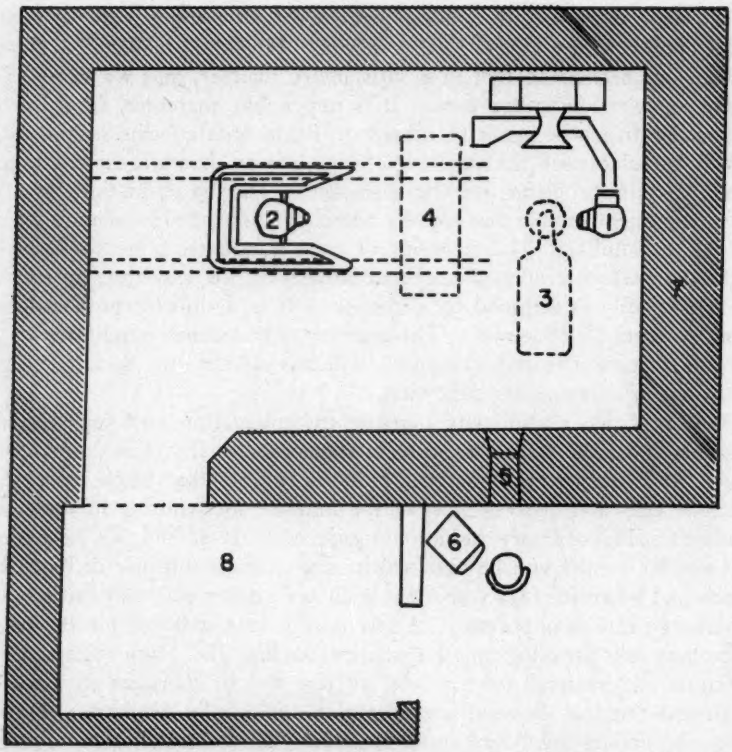

FIG. 7. Facility for simultaneous, uniform irradiation of the entire human body with high energy photons of cobalt 60.

1. Cobalt 60 Teletherapy Unit, Picker X-ray Company, C 1000. This is a usual rotational teletherapy unit with an additional special collimator to give a 2-meter broad beam at a distance of 2 meters as indicated in the diagram 3. The collimator is fitted with a variable lead filter to regulate dosage rates.

2. Cobalt 60 Unit, Picker X-ray Company, C 700. A low specific activity Cobalt 60 unit for general radiation studies, fitted with special collimator as in 1 above.

3. The usual table for positioning patients receiving usual rotational teletherapy treatment over limited areas with Picker unit C 1000. This is moved aside and the rotational head directed away from its shield when the unit is used for total-body radiation.

4. A narrow bed, 36 inches wide and 2 meters long, for patients receiving irradiation of the entire body at dosage rates of 10 to 200 R per hour and total dosages of 200 to 1,000 R, with units 1 and 2 operating as opposed balanced beams, as indicated in the diagram.

5. Viewing portal.

6. Control panel.

7. Heavy concrete walls providing radiation shield for operating personnel (cross-hatched).

8. Entrance maze.

Figure 8 is a chart of laboratory data of a recent patient, a girl of 16, critically ill with acute leukemia,[8] in relapse after current failure of conventional chemotherapy. She was isolated from bacterial contacts, and given a mean tissue dose of 300 r of total body irradiation with an ordinary 250 KV therapy machine, and an infusion of bone marrow from her sister. The irradiation was given by quadrants, upper and lower, front and back, including arms, legs and head. Radiation of this type overlaps in one place and does not penetrate into another, hence one cannot reasonably go to

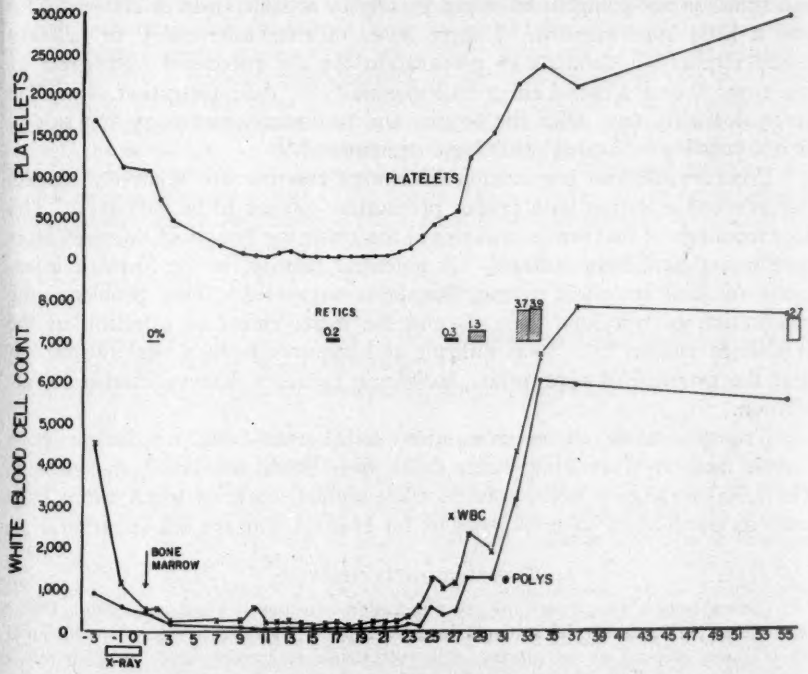

FIG. 8. Chart of hematologic studies of a 16 year old girl with acute leukemia. The patient received 300 r of whole-body irradiation and an infusion of normal marrow from a sister.

higher doses without fear of burning some areas. After irradiation, leukemic cells, normal white cells and the platelets disappeared. Antibiotics and frequent transfusions of fresh blood carried the patient through a bad two weeks of recurrent fever and infection. A normal white count and the platelets returned, and the infection subsided. A normal bone marrow was found on biopsy to have replaced the leukemia. We do not know whose marrow this is. The patient and her sister are of identical blood type. The patient has been in school on no therapy and has remained well for three months. Quite possibly she will have a recurrence, but from her point of view her present well-being is most satisfactory.

Summary

In summary, let us mention that clinical observations such as those just described have been made by other workers—Tocantins [42] in Philadelphia, Andrews [43] in Tennessee, McIlvanie [44] in Spokane, and Atkinson [45] in Pennsylvania. These men have had clinical failures, and so have we.[7, 8] An obvious consideration determining outcome of treatment is the dose of irradiation and the relative radioresistance of the leukemia treated. A resistant leukemia requiring, for example, more irradiation than the intestine can stand, is not going to be helped greatly by a tissue dose of 200 or 300 r and a little bone marrow. Larger doses of irradiation—800 to 1,000 r —are required in animals as preparation for the successful homograft of marrow [2, 41] or for useful effect on leukemia.[37, 38] Administration of similar large doses to man, with the finesse and uniformity necessary for safety, is not possible with usual radiologic equipment.[8, 46]

Procurement and preparation of human marrow are relatively simple. Intravenous injection with proper precaution appears to be harmless. The shortcomings of marrow as a material for restoring lymphoid defenses after irradiation have been outlined. A potential remedy, in the form of injections of fetal lymphoid tissue, has been suggested. This problem—the restoration of lymphoid defenses and the management of infection in the irradiated subject [47, 48, 49]—is difficult and requires further exploration. It and the problem of appropriate radiologic facilities deserve immediate attention.

Transplantation of marrow after lethal total-body irradiation is a simple method of avoiding acute death from lethal radiation exposures in the 1,000 r range in some species. We should know as much about it in man as possible, as soon as possible, for reasons that are self-apparent.

Summario in Interlingua

Le exposition del corpore integre a radiation ionisante del ordine de 500 a 1000 r es sequite per le morte del subjecto in inter septe e 10 dies. Dysfunction medullar es le causa primari de tal mortes, e le symptomas es primarimente sanguination e septicemia. In plure species de animal, morte de iste genere pote esser evitate per le infusion intravenose de homologe cellulas medullar un o duo dies post le exposition al radiation. Le infundite cellulas medullar migra a lor appropriate sitos in le medulla del subjecto irradiate, se divide, se multiplica, e assi restaura le function medullar in tempore pro salvar le vita de ille subjecto.

In recente studios, seligite patientes con leucemia ha recipite doses considerabile de irradiation del corpore total (200 a 600 r) e un infusion de medulla normal ab appropriate cadaveres o ab voluntarios. In certe casos, remission del processo leucemic de grado e duration significative ha sequite iste mesuras. In altere casos le patiente ha experientiate non plus que beneficios temporari. Un obvie consideration in predicer le resultato de un tal tractamento es le dose de irradiation usate e le relative radioresistentia del leucemia in question. Un typo de leucemia resistente que require, per exemplo, un plus grande dose de irradiation que le intestino pote indurar non pote beneficiar grandemente de un dose de 200 o 300 r al histos, combinate con un micre quantitate de medulla ossee. Mesmo in animales laboratorial,

doses plus grande de irradiation—i.e. doses de 800 a 1000 r—es requirite pro le effectuation a bon successo de permanente homograffos de medulla o pro exercer un effecto utile super leucemia.

In rodentes con irradiation inadequate, le graffo de medulla es temporari, sed le medulla del hospite se regenera. Quando le radiation es adequate, le graffo es permanente, e le medulla del hospite non se regenera. Inter le duo—in le vicinitate de 500 r in rodentes e canes—ni le medulla del hospite ni le graffo medullar succede adequatemente, e in iste situation le mortalitate es alte. In homines, le dosage que es ni le un ni le altere debe etiam esser in le vicinitate de 500 r, sed ni su position ni le grado de su importantia ha essite definite.

In subjectos con irradiation adequate, le graffo de medulla pote succeder durante que le morte superveni nonobstante in le presentia de infection intercurrente e un relativemente aplastic systema lymphoide. Ergo, infusiones de medulla restaura le medulla sed non restaura necessarimente le function in irradiate splenes e nodos lymphatic. Ha essite proponite un remedio possibile in le forma de injectiones additional de fetal histos lymphoide. Iste possibilitate se trova sub perscrutation. Le integre problema—i.e. le restauration del defensas lymphoide e le tractamento de infection in le subjecto irradiate—require explorationes additional. Illo merita le attention immediate del expertos. Le mesmo vale pro le problema del elaboration de appropriate facilitates radiologic pro le regulate administration de irradiation uniforme del corpore integre de patientes human.

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THE PATHOGENESIS, DIAGNOSIS AND TREATMENT OF STROKES: A PROGRESS REPORT *†

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FOUR years ago I presented before the Annual Session of the College a brief analysis of the state of knowledge concerning certain major aspects of the problem of strokes.[1] Emphasis was placed on the need for greater interest in this field, which is so important individually, numerically (approximately 2,000,000 persons living today have had strokes, and about 200,000 die each year from this cause), and economically. While major problems in this area remain unsolved, it is with pleasure that we can now recount signs of substantial progress. There has been a great increase in interest on the part of investigators and clinicians throughout this country and abroad. Large funds have become available for research from private, voluntary health agency and governmental sources.

One of the most significant advances has been recognition of the fact that interest in the pathogenesis, diagnosis and treatment of strokes cannot justifiably be compartmentalized within one specialty such as neurology. Rather, if significant progress is to be made, all disciplines which have any light to shed on this matter must be tapped for their total resources. For example, in addition to the neurologist, the pathologist, the brain and lipid chemist, the biochemist, the ophthalmologist, the cardiovascular specialist, those investigating hypertension, atherosclerosis, obesity and endocrine function, the neurosurgeons, the vascular surgeons and many others, have an important and legitimate interest in this field, and they should be urged to contribute their specialized knowledge to the total.[2a] These groups are still too often working as isolated units, thus retarding the free exchange and dissemination of their findings. None has more to offer or to receive from such an interdisciplinary exchange than do the internist and the general practitioner. Following a stroke, the large proportion of patients are first seen by either internists or general practitioners, and the care of most of them remains in their hands. Even more important, these physicians have the opportunity of observing many of these patients for months or years before the first serious episode. Too often in the past this has been a matter of observation without interpretation. Key portents have been missed, and their significance has not been grasped until irreparable, even fatal damage

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has occurred. We are learning more about the importance of the earliest signs, the "little strokes," and the slow strokes. Now we know that something should and often can be done to delay or forestall more serious developments.

Another step of importance has been the development of a new, carefully conceived Classification and Outline of Cerebrovascular Diseases. A Committee, an outgrowth of the first Princeton Conference on Cerebral Vascular Diseases, was established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, and has been functioning under the chairmanship of Dr. Clark H. Millikan. The mission has been to create order out of chaos. The confusing terminology which played havoc with communication has been well codified. It will be published in complete form in *Neurology*[3] and in the *Transactions of the Second Conference on Cerebral Vascular Diseases* this spring.[2b] I commend this to your attention and use.

As suggested above, the limited view that a stroke is strictly a localized neurologic phenomenon should be abandoned. It may be true on relatively rare occasions, such as a hemorrhage into a brain tumor, but in the vast majority of instances a stroke represents a manifestation of a generalized disease process most commonly either atherosclerosis, hypertension or a thrombo-embolic diathesis. Thromboembolism affecting an artery is often secondary to heart disease. With this in mind, the keys to both prevention and treatment have little or no relation to the brain substance itself, which is involved merely by chance, but must rest on the fundamental mechanisms responsible for the development of atherosclerosis, disturbances in the clotting factors, and the pressor factors. We will therefore turn to these phases of our problem.

Major attention has been focused on the development of atherosclerosis during the last few years, and it is attractive to contemplate that when we are able to prevent or reverse this process most of our present tragedies due to heart, cerebral and peripheral vascular diseases will be behind us, although what we will do with the aged population that will then continue to live may prove to be an even more perplexing problem. It has long been known that certain conditions, such as diabetes mellitus, nephrosis, xanthomatosis and primary cholesterolemia, are associated with an accelerated deposition of atherosclerotic material. More recently, we have all been intrigued by the possibility that the so-called normal American serum cholesterol level may in reality be a precursor of accelerated atherosclerosis, and hence of earlier strokes and myocardial infarctions; whereas the lower serum cholesterol levels common to races and nations on low intakes of saturated fats retard or prevent the development of atherosclerosis, with its inevitable consequences.[4, 5, 6] Furthermore, unsaturated fats, especially those with a high linoleic acid content or iodine index, such as safflower oil, corn oil or fish oils, have been shown to reduce the cholesterol levels in the

serum when *substituted* for saturated fats in the diet.[7a, 7b, 7c, 7d, 8a, 8b] Perkins et al.,[9] working in our laboratory, have shown that safflower oil in large doses fails to reduce the serum cholesterol *when added as a supplement* to the normal diet of young males. Additional studies, evaluating other unsaturated fats in various combinations as supplements, are under way.

Are we then on the way to solving the problem of atherosclerosis and, more specifically, strokes secondary to that process? To assume that we are nearing the solution by this approach is unwarranted at present. There are many weaknesses in the structure of this hypothesis, a few of which must be constantly borne in mind. For example, Ancel Keys and his coworkers [4, 6] have demonstrated that certain selected countries can be charted in such a way that the fat in the diet appears to be related to the alleged death rate from cardiovascular disease. However, as Yerushalmy and Hilleboe [10] showed, a wider random sampling involving 22 countries failed to confirm this finding. This study actually showed a closer relation between a high animal protein intake and heart disease. The causes of death as listed in most countries, especially those where nutrition is low, are poorly compiled and documented. Poor documentation is also common, but to a lesser degree, in many areas in this country. Even under the best of circumstances it depends too largely upon clinical impressions, and this audience does not need to be reminded how erroneous they may be.[11] The results of the preliminary epidemiologic studies reported by Bronte-Stewart, Keys, White and others,[4, 5, 6, 13] while not conclusively establishing a relationship between dietary fat intake and atherosclerotic cardiovascular disease, are challenging enough to require more intensive studies, carried out with the thoroughness of the Framingham study which is being conducted by the U. S. Public Health Service.[12a, 12b] It seems logical that the findings regarding the incidence of cerebral artery disease in such studies would parallel those of coronary artery disease, and in general the evidence, although scanty, shows a trend in that direction. However, paradoxic reports from Japan suggest a relatively low incidence of coronary artery disease and a higher incidence of cerebral vascular disease. As often happens, this discrepancy may prove to be apparent rather than actual. Kusakawa [13] has pointed out that in Japan many heart deaths due to coronary artery disease are mislabeled as intracranial lesions of vascular origin. Sudden deaths of older patients are commonly diagnosed as apoplexy without more ado. What this does to vital statistics should be obvious to all. As another example, the Bantu have been considered of especial interest because their diet is notably low in animal fat and cholesterol. Autopsy findings have been quoted as proof of the low incidence of atherosclerosis, with its serious coronary and cerebral complications. This view is supported by Becker,[14] who, in 3,000 autopsies on Bantu, held atheroma to have been the direct cause of death in only 0.4%. These figures were about the same in Edrington's [15] survey of autopsies in West African Bantu. On the basis of these

and other studies, recent teachings have suggested that heart and arterial diseases are very rare among the Bantu. Recently, Laurie and Woods [16] have challenged this view and have reported that (1) aortic atherosclerosis is common, and (2) cerebral vascular disease is relatively common among the Bantu. It is unfortunate that they did not include data in reference to coronary artery disease. The discrepancies are marked and disturbing. Becker reported finding only one cerebral catastrophe in 3,000 consecutive Bantu autopsies, whereas Laurie and Woods found 31 such catastrophes in just under 2,000 consecutive autopsies, *a prevalence almost 50 times greater than Becker's. Among the Bantu medical patients the incidence of cerebral vascular disease was as high as that reported at St. Bartholomew's Hospital in London,*[17] *namely, 3.5%.*

Actually, little attention has been paid to the fact that while Becker reported 0.4% incidence of death from atherosclerosis, he found 74% of the patients over 60 and 56% of the patients over 45 to have atheromatosis of the aorta, of whom 26% had severe atherosclerosis. It seems very doubtful that these or other figures presented from studies of the Bantus represent the true incidence of atherosclerosis, or especially of coronary or cerebral deaths from this condition. Distances are very great, and transportation for most of the natives is difficult, so that the vast majority of the patients who die from these two very common causes of sudden death never get to a hospital. Even more serious is the fact that no death certificate is required for Bantu dying of natural causes, so that no valid record can be made of the cause of such deaths, even on a clinical basis. Natives dying of causes which disable more gradually, such as cancer, parasites, tuberculosis and others, have time to make their way to the hospitals in larger numbers. All hospital figures are weighted by these facts. It therefore behooves us to be extremely cautious about accepting any hypotheses based on so-called "vital statistics" from any countries in which their compilation is so inadequate.

All of this is not to say that the relation of fat intake to development of atherosclerosis may not prove to be a specific one, but rather, that more critical methods of gathering data to support this hypothesis are necessary before it can be established as a fact.

While stress in terms of physical exercise or more rapid heart action seems to encourage local atherosclerosis, we have no real knowledge of what kind of stress, if any, other than hypertension, plays a similar role in cerebral atherosclerosis. Other segments of the arterial tree are subject to movement and stretching not encountered in the cranium. The vessels of the neck are, however, especially subjected to this type of stress, and this may explain the high incidence of carotid and basilar artery occlusion now being recognized.

The lipid patterns in the blood have been related to the estrogenic-androgenic hormone ratio.[18a, 18b] This suggests an intriguing method for

attacking the development of atherosclerosis generally.[19a, 19b] The cerebral vessels should, however, be considered as carefully as the coronary arteries in such a study. If an effective, nonfeminizing estrogenic hormone should become available, we are still faced with the question as to whether the adoption of an unsaturated fat diet, or such a hormone, after a patient has established a pattern of atherosclerosis with perhaps one or more arterial occlusions, will be of any value whatsoever. In other words, can this process be arrested or reversed at that stage? If not, how early in life? Will a limited fat diet over many years deprive the body of essential substances of importance in combating different types of disease? Will the use of even modified estrogens beginning in youth or early manhood affect fertility or other factors of importance? In other words, assuming that these or other methods are developed to the point where they may decrease the incidence of myocardial infarctions or strokes, we must still weigh these gains against the as yet unknown price we must pay. The work of Myasnikov and his co-workers [20] should be carefully studied and rechecked in this country. They reported studies in rabbits which showed that feeding cholesterol with a large intake of phenamine or vitamin D produced a marked increase in the atherosclerotic deposits in the aorta as compared with those found after feeding cholesterol alone. In contrast, the addition of sedatives such as phenobarbital and chloral hydrate or vitamin C resulted in a marked diminution in the development of atherosclerosis. Heparin produced a reduction in the degree of atherosclerosis, whereas Dicumarol had no effect on the results after cholesterol feeding. They suggest the possibility that these changes may in some way be related to the effect of the various substances on stress reactions. This seems possible in relation to the excitants and the sedatives, but not for all the substances tested. Unfortunately, the state of the cerebral vessels was not reported, but their studies, summarized in the January issue of *Circulation,* certainly open up new vistas for exploration.

Next to atherosclerosis, the clotting mechanism of the blood plays the major role in the production of strokes. Local thrombosis is usually superimposed on an area of roughened or thickened intima, and this combination is the most common cause of strokes. However, in the presence of rheumatic heart disease or myocardial infarction, embolism to the cerebral arteries is very common.[21]

Three primary considerations must be borne in mind when considering the pathogenesis of thromboses:

1. Blood is a constantly varying mixture of many components, some of which have undoubtedly not been recognized as yet. In any thrombosing process in vivo, most if not all of these components become involved, and many of them play a dynamic role in the formation of the thrombus.

2. In disease states the development of thrombo-embolic phenomena does not proceed in the orderly fashion suggested by any of the schematic outlines which have been developed for academic or symbolic purposes. All

schematic presentations must of necessity be oversimplified; the whole process is enormously complex. Actually, at the same instant many stages of the process may be taking place—chemical, physical, physiologic and pathologic.

3. The clotting tendency, as measured by clotting time or prothrombin activity as determined from blood drawn from one set of veins, may bear little relationship to the clotting tendency in some other area of the vascular tree in which, for example, tissues may be undergoing serious changes as a result of trauma, infection or cancer. There should be no great surprise, therefore, when a patient has a hemorrhage in one area while he has a thrombosis elsewhere, or when thrombosis or hemorrhage occasionally occurs while a patient is considered to be at the optimal level of anticoagulant therapy as measured by the usual tests of blood drawn from the antecubital veins.

The development of an arterial thrombus usually depends on (1) changes in the wall of the artery which roughen the intima or narrow the lumen, as, for example, with atherosclerosis or thromboangiitis obliterans, (2) changes in physical and chemical constituents which lead to the deposition or concentration of fibrin in the local area, and (3) the adhesion of cellular and other particles to the wall, which then build up to narrow or to block totally the lumen of the vessel. Inflammatory reactions such as are encountered in thromboangiitis obliterans, periarteritis nodosa and local infections produce irregular surfaces which also encourage thromboses. Trauma, whether accidental or surgical, may roughen the intima with the same result. These latter conditions are so rare as etiologic factors for strokes that they will not be further considered in this paper.

The next steps leading to thrombosis are extremely complex and far from fully understood. We are not certain whether the primary action may be physical rather than chemical. For example, it has been suggested that the inner surfaces of the tubes (arteries) may normally have negative (repulsive) charges which tend to keep the components of the blood from adhering to them. The natural anticoagulants, as exemplified by heparin, appear to have fairly strong negative charges. These may aid in keeping certain molecules, notably those of fibrinogen, in a state of mutual repulsion. When conditions change, reducing these negative charges, it becomes easier for the long, slender, rotating molecules of fibrinogen to adhere to each other, producing the sticky fibrin [22, 23] which, in turn, may adhere to the injured wall of the vessel. This enmeshes other components of the blood—first platelets, which in turn contribute to this reaction by the release of thromboplastin, which speeds up the production of more fibrin. Sheppard and others working in our laboratory [24, 25, 26, 27, 28] have explored this field for some years, but much more needs to be done to clarify the physical aspects of this process.

More has been done by countless workers on the biochemical aspects

of the coagulation process. Unfortunately, most of this work had of necessity to be carried out in vitro under conditions which are foreign—although probably somewhat parallel—to those encountered within the walls of the vascular system. The following is a modification of several theories which have been evolved, notably that of Owren:[20]

1. Contact with the surface of the wall initiates blood coagulation by (a) disintegration of platelets and release of platelet lipid thromboplastin factor, (b) activation of the antihemophilic B factor (plasma thromboplastin component or PTC, Christmas factor), and (c) activation of proconvertin (SPCA, factor VII, co-thromboplastin, the stable factor).

2. Tissue injury, such as already described, yields thromboplastin directly. In addition, in vivo destruction in other portions of the body due to cancer or severe infections may apparently increase the concentration of free thromboplastin. In the blood the platelet lipoid factor, the antihemophilic A factor and the activated antihemophilic B factor interact in the presence of calcium to produce thromboplastin.

3. Thromboplastin and proconvertin (factor VII) combine to form convertin.

4. Convertin, together with calcium, produces a minimal conversion of prothrombin to thrombin.

5. This initially formed thrombin starts the accelerator system, i.e., the conversion of pro-accelerin (factor V) to accelerin (factor VI).

6. Convertin and accelerin interact in the presence of calcium to form prothrombinase.

7. Prothrombinase in the presence of calcium accelerates the conversion of prothrombin to thrombin.

8. Finally, thrombin is formed in sufficient concentration to convert fibrinogen to fibrin.

Balanced against these interactions which move in the direction of coagulation are a series of inhibitor reactions which tend to inactivate thromboplastin, proconvertin, convertin, accelerin, antihemophilic B factor, prothrombinase and thrombin. The action of the anticoagulant drugs in support of this inhibition, thus interfering with coagulation and thrombosing, will be outlined later in this paper.

The reactions described may appear to be complicated, but they actually represent a rather crude oversimplification of what actually takes place. Many new factors have been described; some of them may prove to be of importance, but where they fit into the picture is not as yet determined. The problem of communication has been greatly complicated by the understandable but confusing pride of parenthood in nomenclature exhibited by various workers in this field. As a result, most of the factors are known by multiple names—for example, factor VII has been known by some 14 titles. A tower of Babel has thus been erected. An International Committee for the Standardization of the Nomenclature of Blood Clotting Factors

is presently engaged in the difficult task of unscrambling the nomenclature and evaluating the claims for new factors.

The morphologic development of the clot, which might be considered as the end-result of the processes discussed, was described in detail many years ago. The importance of platelets was recognized in 1882,[30, 31] but their mechanism of function and adhesive characteristics have more recently been elaborated by Apitz,[32] M. B. Zucker,[33] H. D. Zucker [34] and H. P. Wright.[35] It now seems clear that the surfaces of platelets are not entirely dependent upon their surrounding medium, but under certain conditions, such as those encountered postoperatively or with marked infection, the products of platelet activity probably escape through their surface and the cell-plasma interface becomes covered with a film of fibrin. This adhesive surface contact film has such viscosity that even though two adherent particles may have a like electric charge, their mutual repulsion may not suffice to overcome the cementing action of the viscous film. In addition, the hydrophilic colloids which are increased in the blood postoperatively act by reducing the surface charges on the cells, and by modifying the positions of the absorbed water on the cell surfaces. The cells are then able to approach each other more closely and, because their electrokinetic potentials are reduced, their surface tension is sufficiently great to overcome their mutual repulsion so that aggregation may take place. Fibrinogen and globulin are potent hydrophilic colloids in this regard, and their increase during postoperative periods may be partially responsible for the increase in platelet adhesiveness. Sludging due to slowing of the blood flow through narrowed channels makes coagulation easier.

Little understood etiologic factors are known to encourage the coagulation tendency. These include the following: cancer of any tissues, but especially cancer of the pancreas, polycythemia vera, familial thrombosing tendency, and individual idiopathic thrombosing tendencies.

Once the coagulation process is started the thrombus propagates from its fixed adherent head, the body later adhering to the wall of the vessel, often becoming almost a portion of it. A fresh thrombus usually has a loose floating tail which grows and represents a source of potential danger as an embolus.

During the last few years interest has been focused on the question as to whether the ingestion of high fat meals produces an increased clotting tendency during the succeeding few hours. This is an intriguing thought, and might be interpolated into the concept that under certain borderline circumstances the scale might be tipped in favor of clotting and a thrombosis occur within the vascular system, including the cerebral or coronary arteries. Duncan and Waldron [36] reported that significant shortening in clotting time did occur after high fat meals. Tulloch, Overman and Wright [37] concluded that these changes were due largely to artefacts in the technic used. Later Waldron and Duncan [38] and Buzina and Keys [39] published data which they

felt were significant and confirmed significant changes. Borrero et al.,[40] working in our laboratory and using exceptional care with the technic, once more reported data showing no significant changes after a meal containing 1,000 calories of fat, as compared with control readings. All of these studies have been made using the Lee-White coagulation test which, while useful clinically, provides only a very crude estimate under the best of conditions. O'Brien,[41] using the stypven test, has noted some changes but is uncertain regarding their clinical significance, and there is some question as to whether the stypven test does indeed measure the clotting time or the lipid content of the blood. Recently Sheehy and Eichelberger,[42] of the Army Medical School, using the more objective thrombo-elastographic technic, have failed to find any significant evidence of an increased clotting tendency. While the last word has doubtless not been heard on this subject, the present evidence casts very serious doubt on the premise that the amount of fat ingested in even a heavy meal affects the clotting of the blood to any degree capable of precipitating thrombosis. Further refinements in technic may make it possible to measure significant changes in new clotting factors, but this is yet to be established.

On the other side of the coin is hemorrhage as a cause of strokes. It is commonly stated or implied that most hemorrhagic strokes are massive. This is far from the truth. Autopsy studies readily show that innumerable small hemorrhages are frequently found which produce minor clinical signs or none at all. The degree of hemorrhage depends on several sets of factors. Most common among these are: (1) hypertension increasing the stress on the vessel walls and the pressure behind the first leak, which encourages a massive hemorrhage; (2) weakness in the arterial wall on the basis of congenital changes such as aneurysms, arteriovenous anastomoses and, most commonly, atherosclerosis. There are numerous rarer causes; (3) changes in the clotting mechanism which encourage hemorrhage and interfere with the normal protective mechanism which plugs a small leak preventing clinical signs from developing. Thus a major hemorrhage may develop. Such hemorrhagic conditions include blood dyscrasias such as leukemia, thrombocytopenic purpura hemorrhagica, toxic purpuras, and excessive heparin or hypoprothrombinemia as a result of anticoagulant therapy or severe liver disease; (4) hemorrhagic infarction secondary to thrombosis or embolism. This characteristic reaction to sudden arterial or venous occlusion, wherever it occurs, may frequently be retarded or controlled by the tone of the surrounding tissue, such as skeletal or heart muscle. Because of the quality of brain tissue, this inhibiting factor is less active and the degree of hemorrhage must depend on other factors, some of which have been enumerated above. One of the most difficult questions with which we are presently confronted is whether anticoagulant therapy will aggravate the degree of hemorrhage in an infarction. The evidence on this point is not complete and it is conflicting. Studies of this question in reference to myocardial

infarction by Blumgart [43] and others have shown that the infarcted area was not more hemorrhagic or larger in dogs on anticoagulant therapy than in those not on such therapy. Recently two studies of cerebral infarcts have been reported. One report by Frazier et al.,[44] of the Mayo Clinic, indicated that no significant increase in hemorrhage was noted in the experimental infarcts of anticoagulated dogs. However, two of the anticoagulated dogs did develop "freak hemorrhages" into their infarcts, and one hemorrhage was into the ventricles. The other study, by Sibley et al.,[45] of Western Reserve Medical College, resulted in the conclusion that there was an increase in hemorrhage in the anticoagulated dogs. Clinical observation on more than 100 patients started on coumarin derivatives within a few hours after the onset of a stroke has shown rare if any increase of bleeding at least as evidenced by spread of neurologic findings. These drugs do not, however, produce a significant anticoagulant effect for 30 to 72 hours, and this delay may in itself be a protective factor. In other words, the immediate effect of heparin, so frequently desirable, may in this situation be harmful. Our present technic, therefore, is to give coumarin derivatives, usually Dicumarol or Liquamar (although others may be used), without heparin if the patient is seen promptly after his stroke. The treatment is initiated with subcutaneous heparin (75 to 100 mg. at eight- to 12-hour intervals) for two days only if three or more days have passed before the patient is treated. The use of fibrinogen (plasmin) as an adjunct to aid in the prompt disintegration of early soft thrombi is now being studied and may well be more widely used in the future, especially if the pyrogenic reactions common to the present preparations can be eliminated.

The diagnostic and therapeutic problems may be divided into two phases in which the situations to be faced are quite different. The diagnosis in the early phase of intermittent basilar and carotid artery syndromes is sometimes confusing, but has been described in detail in reports by Millikan and Siekert [46a, 46b, 46c] and from our own laboratory.[1, 47] It is most important to establish the diagnosis because of the excellent therapeutic response to anticoagulant therapy as reported by the above workers and by Fisher.[48a, 48b] The mechanism of strokes due to involvement of the cerebral arteries or elsewhere in the brain is often more difficult to establish. In general, the combination of normal blood pressure, previous evidence of occlusive arterial disease anywhere in the system and a clear spinal fluid, together with lack of intracranial pressure signs, may be considered as strong evidence of thrombosis or embolism. Nevertheless, autopsies in such cases have occasionally shown either free hemorrhage or a hemorrhagic infarct. Treatment with anticoagulants therefore constitutes a calculated risk.[49a, 49b] In our clinical experience over a 12-year period this risk has been small enough to appear to justify the treatment in carefully selected patients, but we are not satisfied with such an evaluation, and have therefore set up comprehensive coöperative studies at Bellevue Hospital on the services of the Cor-

nell, New York University and Columbia Medical Schools in which carefully controlled series are being studied with and without anticoagulant therapy. This study will continue for some years, but among other questions it should answer are whether such immediate treatment for acute thrombosis or embolism is helpful, ineffective or harmful, and, if helpful, what the calculated risk is. Careful autopsy studies will serve as a check and thus strengthen our diagnostic technics as related to patients with fatal lesions. Since most patients survive one or more strokes, we unfortunately have no definitive check on their diagnosis but must observe most critically for evidence of extension or worsening of their condition, whether on or off of therapy. Frequently these signs are quite clear and can be tabulated for analysis. Subtle changes may elude us, although diagnostic acumen sharpens remarkably in those especially interested in any field of medicine. When the evidence is clearly in favor of an embolism, therapy should be directed at the mother thrombus, usually in the left side of the heart, as well as the embolus. Even in the presence of a threat of a hemorrhagic infarct, the risk of additional and more serious emboli must be considered. The risk of hemorrhage may prove to be greater when the damaged area is near the meninges, which are very high in fibrinolysin content as compared with other tissues.

After the first few weeks the decision must be made as to whether the patient should be kept on long-term anticoagulant therapy. We now have more comprehensive data on the risk of further thrombo-embolic episodes while on and off of anticoagulant therapy. This has been recently reported in the *Journal of the American Medical Association*.[47] Using a series of 90 patients as their own controls, we have found that during 2,824 patient months without therapy, 74 patients developed 229 thrombo-embolic complications, of which 67 were cerebral. While on anticoagulants, 33 of these same 90 patients during 2,291 patient months developed 72 thrombo-embolic complications, of which 16 were cerebral. Of these, 20, including five cerebral, occurred when the nearest prothrombin time was below 20 seconds —in other words, below optimal therapeutic levels.

These figures seem to indicate that such therapy gives a marked long-term protection, but in order to subject this as well as the acute phase to another type of evaluation, our group has joined with Massachusetts General, University of Pennsylvania Medical College, Jackson Memorial Hospital at the University of Miami, Duke University School of Medicine and the University of California Medical Center in a coöperative evaluation study under the chairmanship of Miller Fisher, of Harvard.

It can be seen from the number of national groups and local comprehensive studies under way that where knowledge is lacking serious efforts are being made to obtain it, and this should bring many definitive answers during the next few years. Meanwhile, clinicians will have to evaluate the reports that are continuing to appear, match the findings in their par-

ticular patients against those discussed in the reports, and use their best judgment.

In the comprehensive study at Bellevue the rehabilitation program is also being subjected to a critical alternate case evaluation. The psychologic aspects, especially those tied into motivation for recovery, are under scrutiny by both psychologists and psychiatrists. Why do some patients have great motivation to get well and strive with such determination and courage, while others, no worse off physically, have a continuing negativistic and defeatist attitude? Is it because of the location and degree of brain damage? Is it because they have never possessed the courage to face up to such a serious crisis? Do some feel that their lives are finished and that they have no future, and therefore withdraw or wish to die? Is it because their home or work environment is hopeless or unpleasant and that their invalidism in reality offers an escape? Will a well planned and progressive rehabilitation program during the first few months after a stroke favorably affect the capacity of the patient to make a good recovery or adjustment? This may seem logical, but is this actually the case? Or is it just apparent, the good results being due to inherent motivation and something worth while to return to, such as work, a good home, and true love and affection from people who care? Will psychiatric evaluation and advice contribute to a favorable result? These aspects have never, so far as we know, been submitted to a sufficiently critical study and analysis, and, although admittedly difficult, this is being systematically undertaken.

Hypertension constitutes a major factor in the production of strokes due to hemorrhage. It would appear desirable to lower the patient's blood pressure. It is often too late to accomplish much by this approach after the brain has been damaged by massive hemorrhage. Therefore, attention should be directed to the lowering of the pressure as a preventive measure. Recently we have new and frequently effective tools for this purpose. These include the rauwolfia compounds and various types of blocking agents. For cerebral vascular disease, however, these must be used with great caution. Too sudden and profound a drop in pressure may result in a sharp decrease or cessation of blood flow through diseased arteries, with the development of a temporary or irreversible ischemic pattern and the signs of a stroke on this basis. This may also occur in other organs, notably the kidney, but the brain is especially vulnerable. Thus we are confronted with a dilemma which calls for skill and caution.

It is regrettable that we do not at this time have many other forms of therapy which can be considered as of established value. Blocking of the stellate ganglion has been largely discarded.[2] Steroid therapy has few advocates for use in the acute phase. Its only value appears to be in the later stages, when the combination of mild euphoria and decreased stiffness and aching may encourage increased effort by the patient. The vasodilating drugs for general use are singularly ineffectual in their action on the cerebral

vessels.[2] More comprehensive studies of their use by direct injection into the carotid arteries are indicated. CO_2 will increase cerebral blood flow while it is being used, but we still do not know whether the blood with a higher content of CO_2 is beneficial, or whether it should be used intermittently or continuously for clinical purposes. This area should be explored more completely.[50] Surgery in this field is in its infancy, but definite advances are being made. For subdural and extrameningeal hemorrhages the results are often spectacular, and they constitute definite indications for surgery. Here the early and correct diagnosis by the first physician to see the patient may be life-saving. For certain arteriovenous anastomoses, small and located in favorable areas, surgery may sometimes be successful. Oliverona and Riives [51a, 51b] demonstrated that surgical excision may in some cases be feasible but, like arteriovenous fistulae and aneurysms elsewhere, many in the brain cannot be successfully treated. Therefore, ligation of the carotid artery has been widely advocated and used. Svien and Hooker [52] have recently reviewed the literature and experience, including that of the Mayo Clinic with this procedure, and have concluded that it is rarely beneficial and occasionally is harmful. The ligation lowers the pressure in the region of the lesion, which results in shunting of blood normally supplying other portions of the brain into the lesion.

On the other hand, DeBakey and his co-workers,[53] Lyons and Galbraith [54] and others have now reported increasing success in the surgical treatment of intermittent strokes based on partial or segmental occlusion of the carotid artery. Emphasizing the segmental characteristics of many of these lesions, they have used synthetic grafts with challenging results. Cooley [55] has also reported a successful endarterectomy with removal of a large arteriosclerotic plaque at the bifurcation of the carotid artery. These must be regarded as pioneering achievements, and such technics will doubtless be more widely developed in the future. Surgery for massive hemorrhage is now being attempted, with some encouraging results, by Botterell, Gurdjian and Bucy,[56] but this is far from satisfactory for most patients, even in the hands of skilled neurosurgeons or vascular surgeons. Hypothermia has now been introduced as a valued adjunct to this type of cerebrovascular surgery. When we look back to the state of heart surgery 15 years ago and compare it with the present, we can feel encouraged and predict that, with increased interest and improved technics, vascular surgery of the brain will show great strides in the next decade.

This progress report indicated many important steps which help the patient of the present and promise more help for the future. It is the fashion now to proclaim each advance in medical knowledge, however minor or remote from patients, as an important "breakthrough." This should probably be reserved for the most significant of discoveries. Progress in a field such as this is more likely to be made by inching ahead along a broad front,

but a true "breakthrough" may occur at any time in certain areas such as atherosclerosis, hypertension or antithrombosing substances.

Summary

The study and treatment of cerebral vascular diseases can no longer be compartmentalized within one specialty such as neurology. In fact, strokes are not primarily lesions of the brain, but usually represent a localized manifestation of a generalized condition, most commonly either atherosclerosis, hypertension, or a disorder of the clotting mechanism. Many specialties have a legitimate interest, including lipid chemists and other biochemists, ophthalmologists, roentgenologists, those studying atherosclerosis, hypertension and blood coagulation, vascular and neurosurgeons and many others.

The relation of the amount of saturated fats ingested to the development of strokes is not established, and much further work needs to be carried out in this area. It is doubtful that a high fat meal increases in any significant measure the risk of intravascular thrombosis.

The use of anticoagulants constitutes an important contribution to the treatment of transient or "little" strokes due to partial occlusion of the carotid or basilar arteries. They appear to influence favorably the long-term outlook for patients after the first stroke. Additional studies are being carried out to refine the diagnosis further and to evaluate the risks of this treatment, especially when used during the acute phases of a stroke involving the cerebral arteries and other branches passing through the brain substance. Venous thrombosis should also be considered more frequently in analyzing the pathogenesis of strokes. New surgical technics are being used for the treatment of massive brain hemorrhage, and for prosthetic by-passing of segments of the carotid arteries when they have developed occlusion. These and other surgical approaches are pioneering but important forerunners of the future. Rehabilitation and psychiatric care are being subjected to more critical scrutiny and evaluation but, pending the results, it seems justified to apply the principles of both very early in the treatment of the patient.

Comprehensive and coöperative studies are now under way which should produce answers to many of the problems which remain unsolved.

Summario in Interlingua

Le studio e le tractamento de morbos cerebro-vascular pote non plus esser considerate como le negotio de un disciplina special, como le neurologia. De facto, attaccos apoplectic non es primarimente lesiones cerebral; usualmente illos representa manifestationes localisate de un condition generalisate, le plus communmente de atherosclerosis, de hypertension, o de un disordine del mechanismo coagulatori. Varie specialistas es legitimemente interessate in le thema, incluse le biochemicos, ophthalmologos, roentgenologos, expertos in atherosclerosis, hypertension, e coagulation sanguinee, angio- e neurochirurgos, e multe alteres.

Le relation del quantitate de grassia saturate in le dieta con le disveloppamento

de apoplexias non es establite, e multe labores additional debe esser executate in iste area. Il es dubitose que un repasto ric in grassia augmenta a grados significative le risco de thrombose intravascular, comparate con repastos isocaloric de hydrato de carbon o de proteina.

Le uso de anticoagulantes constitue un importante contribution al tractamento de transiente o "micre" apoplexias debite al occlusion partial de un carotide o de un arteria basilar. Il pare que anticoagulantes exerce un influentia favorabile super le prognose a longe vista in patientes qui ha suffrite lor prime attacco apoplectic. Studios additional es in progresso pro raffinar le diagnose additionalmente e pro evalutar le risco de iste forma de tractamento, specialmente quando illo es usate durante le phase acute de un attaco in que le arterias cerebral e altere brancas passante per le substantia cerebral es interessate. Thrombosis venose deberea etiam esser prendite in consideration plus frequentemente quando on determina le pathogenese de un apoplexia. Nove technicas chirurgic es in uso in le tractamento de massive hemorrhagias cerebral e pro le circuition prosthetic de segmentos de carotide quando illos ha disveloppate un occlusion. Iste e altere mesuras chirurgic es precursores initiatori del futuro. Le methodos de rehabilitation e del adjuta psychiatric es sub scrutinio e re-evalutation critic, sed—usque le resultatos de tal effortios es cognoscite—il pare justificate applicar le principios de ambes multo precocemente in le curso del tractamento.

Comprehensive studios cooperative es nunc in progresso. Ab illos on pote expectar responsas a multes del problemas que remane sin solution.

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SPONTANEOUS STROKES IN THE YOUNG*

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THE spontaneous occurrence of cerebrovascular accidents in normotensive healthy individuals is contrary to the conventional notion that arteriosclerotic and occlusive vascular disease of the brain is a phenomenon of old age. Yet strokes in the young are not rare. Thirty-two such cases in young adults and two in children have been encountered by the author in private neurologic practice in the last seven years.

Acute hemiplegia and other focal neurologic manifestations characterize this group. The ages range from five and one-half years to 45 years, the arbitrary cut-off point of this selection. No cases are included that had traumatic, infectious, neoplastic, hypertensive, vascular or any other disease. All subjects were ambulatory and active. Most of the patients were white-collar workers, representative of the population of Washington, D. C., and its immediate environs. No Negro patients satisfied the criteria for the group. Institutionalized patients, including those from veterans' hospitals, were eliminated from this sample.

Although the precise etiologic mechanism was not always established, two large categories of strokes in the young could be recognized: those due to venous and those due to arterial thrombosis:

1. Cerebral Venous Thrombosis
   (a) Infantile hemiplegia.
   (b) Puerperal hemiplegia.
   (c) Venous thrombosis of pregnancy.

2. Cerebral Arterial Thrombosis
   (a) Carotid artery.
   (b) Middle cerebral artery.
   (c) Other arteries of the circle of Willis, single or in combination.

Infantile hemiplegia, a well recognized syndrome, is characterized by sudden onset of hemiplegia, often with convulsions in children less than one year of age. It is due to venous or sinus thrombosis. It may occur spontaneously, but almost always is associated with fever or dehydration. Twenty such cases have been encountered and are the subject of a separate paper.[1]

Puerperal hemiplegia is probably the most common form of spontaneous

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stroke in healthy women. It is characterized by the sudden onset of headache, convulsions, hemiplegia or other focal neurologic signs during a previously healthy puerperal period. It appears from several hours to several weeks post partum and is due to cortical venous thrombosis. The clot may propagate to other veins or to the dural sinuses. The precise mechanism is unknown, and it is only in recent years that this condition has been recognized during life.[2] Twelve such cases have been observed, eight of which have been previously reported.[3] All recovered, and there have been no recurrences. Three patients have had subsequent pregnancies and deliveries without complications. Minor neurologic sequelae persist in three of the 10 cases.

The following typifies this group:

Case Report

Case 1. A 24 year old primipara suddenly developed severe headache, aphasia, convulsion, and coma two and one-half weeks after a normal delivery. A lumbar puncture showed clear xanthochromic fluid with a protein content of 132 mg. %. Other studies were negative. The patient showed gradual improvement and was discharged from the hospital three weeks after the cerebrovascular accident. When examined one year later the neurologic examination showed a right upper visual field cut, slight increase in the tendon reflexes in the right arm, slight facial weakness, and aphasia. The latter was of a mild degree, but there was marked dyslexia. The above defects have remained static over a period of five years. Figure 1 represents the permanent visual field defect.

As stated, the etiology of the above cerebrovascular accident is a venous thrombosis which frequently is associated with convulsions and coma. A moderate amount of blood in the spinal fluid is present in about half of the cases. The prognosis is good for survival, morbidity is low, and conservative treatment is indicated.

A similar but less common affliction occurs during early pregnancy. Two such cases have been encountered. Surgery may be indicated where intracranial pressure remains at high levels. In one such instance, temporal decompression was a life-saving measure.[4]

This group of "strokes" accompanying gestation and parturition should be segregated from the cases due to arterial occlusion, and also should be distinguished from a large number of diseases that simulate the puerperal hemiplegia and venous thrombosis of pregnancy. Eclampsia is probably the most frequent erroneous inference. Treatment for the latter condition would be contraindicated in puerperal hemiplegia. Principles of treatment and other data have been outlined in a previous report.[3]

In contrast to the three subgroups due to cerebral venous thrombosis, strokes in healthy active individuals may occur from arterial occlusion. Sixteen such cases under 45 years of age were selected. The youngest was a five and one-half year old girl who suffered a spontaneous carotid artery thrombosis and recovered without any residuals. One 13 year old child

FIG. 1. Permanent visual field defect in case 1; sequela of puerperal hemiplegia.

still has a left hemiparesis five years after the acute episode.[5] In the adult cases the ages range from 23 to 44 years (table 1). This last group constitutes the main substance of this paper.

TABLE 1

Age	No. of Cases
21–25 years	3
26–30	3
31–35	3
36–40	4
41–45	3

The degree and pattern of acute neurologic involvement in these 16 cases varied, and included complete hemiplegia, aphasia, homonymous hemianopsia, hemihypesthesia and thalamic syndrome. Most attacks were relatively brief, lasting several hours to several weeks, and usually with minimal sequelae. None died. The worst residual was a hemiparesis associated with a mild convulsive disorder. Homonymous hemianopsia and field defects persist in three men, unilateral optic atrophy in two women. One 28 year old man suffered a recurrence of aphasia and hemiparesis two years after the first attack, with no sequelae after 24 hours and no symptoms three years later. Transient brief recurrences appeared on two occasions in one patient, and on three occasions with another. Eleven of the patients have been followed for three years or longer. The following case typifies this group:

Case 2. In 1950 this 37 year old, left-handed normotensive Government worker suffered a sudden attack of aphasia and paresthesia in the right hand, arm and face. Several hours later the leg, face and arm became paralyzed, but with resolution of the paralysis over several hours. Over the next several months these attacks recurred, lasting several minutes, sometimes associated with blurring of vision and vertigo. There was frequent left-sided headache. The patient was hospitalized and elaborate studies were instituted including an electroencephalogram, arteriogram and pneumoencephalogram. All were negative, and the patient was discharged asymptomatic and has remained so since.

Although the negative arteriogram as well as the pattern and sequence of the symptoms in the above patient could represent a basilar artery insufficiency or thrombosis, the complete disappearance of his symptoms would argue against this inference.

Other nonvascular lesions, e.g., multiple sclerosis and tumor, demand consideration in this and the other cases, but the focality, course and negative laboratory studies favor a benign vascular lesion. Headache, which is uncommon in multiple sclerosis, occurred contralateral to the hemiparesis in nine cases. In one case headache was a particularly conspicuous feature:

Case 3. On February 25, 1954, a 25 year old Government worker suffered sudden onset of dysarthria and confusion, with weakness of the right hand. A right Babinski's sign was elicited. In the next several days all manifestations resolved except headache and tenderness to percussion over the left frontal area that persisted

for several weeks. He was asymptomatic except for transient recurrence of intermittent headache during the month of January, 1957. All laboratory tests, including visual fields, electroencephalogram, spinal fluid examination and pneumoencephalogram, were negative.

Carotid arteriography was not done in this last case. Nor was it done in most instances because of the hazard of precipitating or exacerbating a hemiplegia in an already susceptible patient.[6-10] Further, the indiscriminate use of arteriography is not justified, since the diagnosis of carotid artery occlusion often can be made on clinical grounds. Moreover, the arteriogram does not always reveal occlusion of cerebral vessels. In the five cases of spontaneous unexplained strokes reported by Sprofkin and Blakey[11] occurring in patients aged 32 to 39 years, two arteriograms were normal, and one showed occlusion of a branch of the left middle cerebral artery. Arteriograms were not done in the other two cases, but thrombosis of the middle cerebral artery, cause unknown, was inferred. A similar group of 13 patients was found by Berlin[12] to have normal arteriogram in seven patients. In four other cases there was evidence either of narrowing or of occlusion of the internal carotid artery or its branches.

It is quite possible that many of the spontaneous strokes in young healthy individuals would reveal carotid artery occlusion by arteriography. A positive carotid arteriogram certainly establishes incontrovertible evidence of cerebrovascular occlusion, and the statistical probability of complications with arteriography is not great and is perhaps minimal in the young patient. But clinical evidence of thrombosis should be marshalled and the test circumvented when possible, especially since the rationale of modern therapy does not compel the clinician to pinpoint precisely the locale of the cerebral thrombosis. As indicated, the arteriogram is often normal, and it is sometimes ambiguous.[9] Thus responsibility for refining the diagnosis of strokes in the young reverts to the clinician, on whom it rested before Moniz introduced arteriography in 1927. The cardinal sign of carotid artery thrombosis consists predominantly of hemiplegia. It may be sudden, or it may be ushered in by repeated brief, stereotyped unilateral episodes of transitory weakness, paralysis, numbness, aphasia and homonymous hemianopsia, extending over an interval of days or weeks. Contralateral headache is usually present. Neurologic examination may reveal decreased palpability or tenderness of the carotid artery on the side contralateral to the weakness. To confirm the diagnosis of carotid artery occlusion, Webster, Gurdjian and Martin[13,14] recommended digital compression of the uninvolved carotid artery. If syncope occurs due to resulting cerebral anoxia, carotid artery occlusion is inferred. This procedure is not without risk.[10]

Horner's syndrome and homonymous hemianopsia are the most common ocular signs of carotid artery thrombosis. The hemianoptic defect is often characterized by relative sparing of the upper quadrants of the defective half fields, since the superior portions of the optic radiations are supplied by the

middle cerebral artery, while the lower portions are supplied by the posterior cerebral artery.[15]

Unilateral impairment of visual acuity and optic atrophy occur occasionally, as in two of the 16 cases. Transient and permanent psychiatric syndromes have been found also.[6, 9, 16, 17]

A further useful and relatively simple test is ophthalmodynamometry, described by Bailliart in 1917 [18] and by Magitot in 1922,[19] and more recently recommended by Wood and Toole.[10] A small calibrated plunger is applied to the sclera of the outer canthus. The retinal artery is visualized through a conventional ophthalmoscope as progressive pressure is applied to the plunger. The diastolic pressure is read when the retinal artery begins to pulsate, and the systolic pressure when pulsations again disappear. Pressure readings in the two eyes are compared, and since the retinal artery reflects internal carotid artery pressure, the lower pressure is found on the side of the carotid artery occlusion. According to van Allen et al., when symptoms of carotid artery occlusion are confirmed by ophthalmodynamometry, "direct surgical exploration of the artery without preliminary percutaneous angiography may prove to be the best judgment." [20]

It is often impossible on clinical evidence alone to distinguish between middle cerebral and carotid artery thrombosis. The presence of Horner's sign with contralateral hemiplegia and decreased pulsation of the carotid artery establishes the latter on clinical grounds, as in the following two cases.

Case 4. A 35 year old healthy man had a sudden onset of right hemiplegia and profound aphasia on February 19, 1958. Neurologic examination two days later at the George Washington University Hospital revealed a complete right-sided flaccid paralysis, with pyramidal tract signs on the right. The left carotid artery was tender and less palpable than the right. There was left-sided ptosis, enophthalmos, miosis and anhidrosis. A diagnosis of left internal carotid artery thrombosis was made, confirmed by arteriography (figure 2). Spinal fluid was completely normal. Anticoagulants were prescribed. Improvement continues, but the prognosis appears to be less favorable than in the other cases.

Case 5. On January 18, 1957, a 39 year old housewife suffered severe left-sided headache that kept her awake most of the night. This gradually disappeared and she was quite well until 9 a.m., when, while sitting in her car, she suddenly noted that she was unable to speak. She yawned and seemed sleepy, and her husband noted facial asymmetry. There was no loss of consciousness and no convulsions, and she remained ambulatory. She was admitted to the George Washington University Hospital on January 19, 1957. Blood pressure, 120/70; pulse, 120; temperature, 37° C. The neurologic examination showed complete aphonia, alexia and dysgraphia. There was right facial weakness, the tongue deviated to the right, and the deep tendon reflexes were increased in the right arm. The left lid showed slight ptosis, and the left pupil was miotic. The left carotid showed decreased amplitude of pulsations.

Spinal fluid examination showed 26 lymphocytes, protein of 14 mg. %, and a flat colloidal gold curve. Serologic tests were negative. Skull x-ray, electrocardiogram and complete blood count were normal. The aphonia changed to aphasia in three days; the latter gradually receded over the next several months, until the present, when it is scarcely detectable. The carotid pulse is still diminished on the left.

Arteriogram was not recommended, since the diagnosis of left carotid artery thrombosis was warranted on clinical evidence. This last patient was started at once on anticoagulant therapy, a measure which seems justified according to recent observations and authoritative opinions.[21, 22]

FIG. 2. Arteriogram showing internal carotid artery occlusion in case 4.

Surgical measures were not recommended in the light of the favorable outcome observed with conservative treatment in nearly all of the previous cases of cerebral thrombosis noted above. Surgery on the carotid artery is still in an investigative stage,[20] but may evolve into a safer and more satisfactory procedure in the future. The increasing number of reports on various technics from several centers appears promising.[10, 13, 23, 24] Jackson and Fromm recommend caution in interpreting the results of current surgical therapy.[25]

The cause of cerebral arterial thrombosis is atheromata, analogous to if not identical with the atheromatous process that occurs in coronary vessels and elsewhere. Some studies suggest that the cerebral artery is more vulnerable to atheromatous plaque formation because of certain inherent structural weaknesses.[26]

Plaques that cause strokes in the young, healthy, normotensive patient are probably solitary. This assumption seems plausible, since none of the patients died, residuals were uncommon, and all except case 4, whose follow-up period is too brief, are engaged in productive activity. None has shown electrocardiographic changes or other evidence of progressive vascular disease. None had diabetes, subarachnoid bleeding or syphilis. The electroencephalogram was normal in six cases and abnormal in two, including the one patient with residual hemiplegia (case 4, figure 3). The other patient has no clinical residuals (figure 4).

As in coronary artery occlusion in a comparable age group, the patients were predominantly male (11 out of 16). In the 10 case summaries of cerebral thrombosis in young adults reported by Berlin, only one was a female. Carotid artery occlusion also occurs predominantly in males.

Stress has been blamed for increasing the susceptibility to or precipitating coronary thrombosis, and similar mechanisms have been invoked for cerebral thrombosis.[27, 28] In six men there was a definite history of acute stress, associated with excessive smoking in five. One woman had been under chronic duress for several months prior to her stroke. The psychodynamics of these patients were not explored, but there was no indication of "fulfillment of unconscious masochistic needs," as suggested by Seidenberg and Ecker [27] as a possible etiologic factor in cerebral thrombosis in the young.

Only two patients (the two most recently encountered, cases 4 and 5) received anticoagulant therapy. In case 4, cerebral infarction probably occurred abruptly, thus limiting and nullifying the value of anticoagulants. Extension of the clot might have been prevented or minimized by the therapy, but this is speculative. The role of anticoagulants in cerebral thrombosis requires more and better controlled data. The experience with this selected group of 16 patients justifies the assumption that prognosis is good for cerebral thrombosis in young healthy normotensive patients, with no treatment. If anticoagulants, stellate blockade or other therapy had been employed, a nonvalid cause-and-effect relationship might have been deduced.

In the present state of uncertainty it seems reasonable, on inferential evidence,[21, 22] to employ anticoagulants if cerebral (arterial) thrombosis has occurred or is threatening. Millikan and others [22] have documented their arguments for this measure, but insist on restricting anticoagulant therapy to four groups of patients, those with (1) intermittent insufficiency in the vertebral-basilar system; (2) intermittent insufficiency in the carotid system; (3) thrombosis in the vertebral-basilar system with infarction, and (4) actively advancing thromboses in the carotid system.

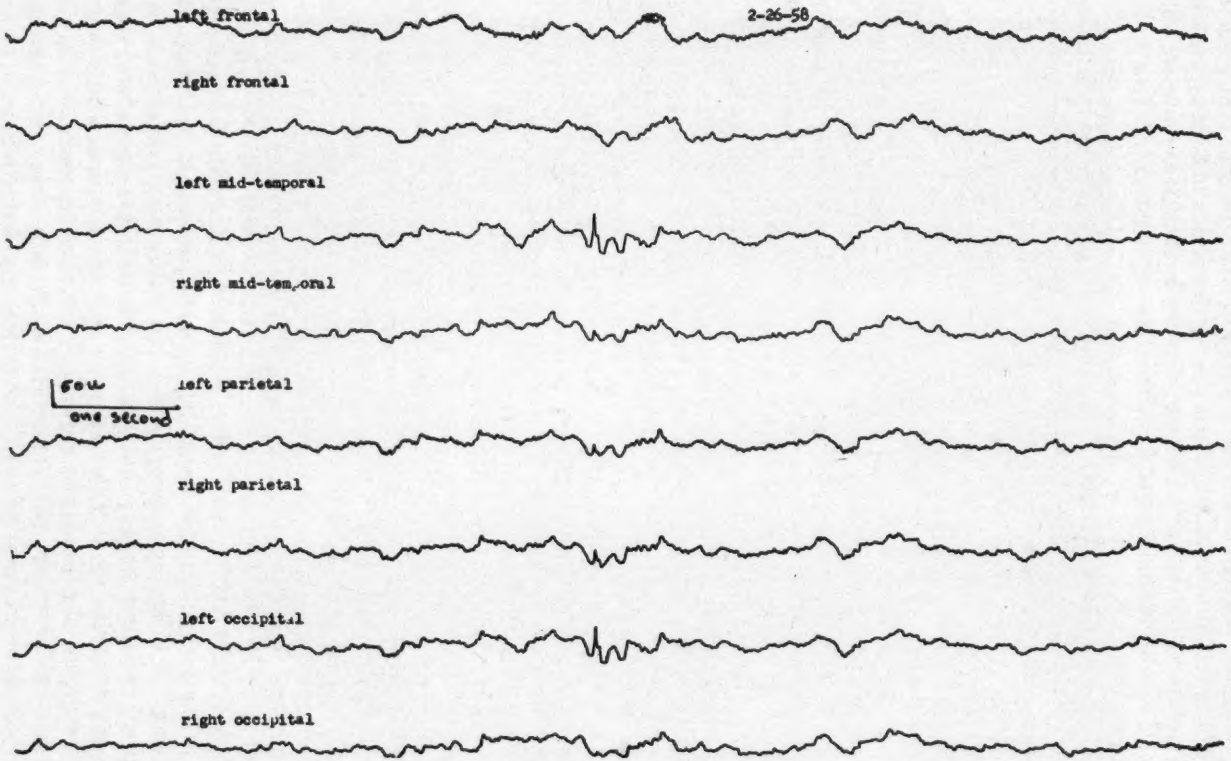

FIG. 3. Electroencephalographic specimen from case 4, showing spike focus in left midtemporal and occipital area.

FIG. 3. Electroencephalographic specimen from case 4, showing spike focus in left midtemporal and occipital area.

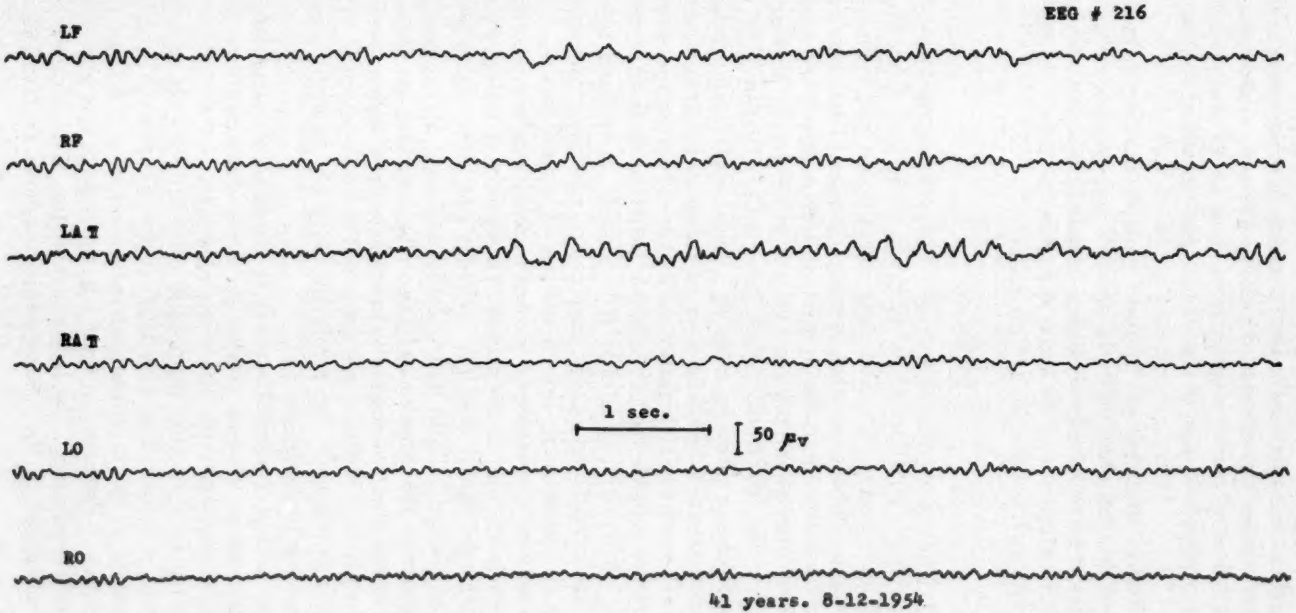

FIG. 4. Electroencephalographic specimen with left anterior temporal slow wave focus in a 41 year old man who had acute onset of aphasia and dyslexia with increased reflexes on the right side. No clinical sequelae.

Anticoagulants were not used in the 12 women with puerperal hemiplegia due to cerebral venous thrombosis. Mortality was zero, and sequelae were rare, over a follow-up period ranging from three to 15 years. Expectant treatment is justified by the circumstances and statistics of this unique condition.[8]

Thus, effective treatment of "strokes" requires exacting refinement of diagnosis, and detailed attention to the patient's age, presence of underlying cardiovascular or thrombo-embolic disease, metabolic disorders, malignancy, subarachnoid bleeding, site of the lesion and other variables. A stereotyped therapeutic approach is hazardous to the patient.

Summary

The occurrence of spontaneous strokes in healthy normotensive young subjects is not rare, as witnessed by 32 cases whose ages range from five and one half to 44 years. No cases were included that had traumatic, neoplastic, infectious, embolic or other primary disease. Two large etiologic groups were identified, those due to cerebral venous thrombosis, and those due to cerebral arterial thrombosis. Of the latter group, 16 cases were observed, some due to carotid artery thrombosis. Diagnosis of carotid artery thrombosis can often be made by clinical observation, including a history of acute onset of headache with contralateral hemiplegia, and ipsilateral Horner's syndrome. Palpation of the carotid artery and ophthalmodynamometry are valuable but not infallible technics that deserve more frequent usage. Arteriography is often indispensable, particularly to exclude intracranial aneurysm or tumor, but unnecessary, painful or dangerous tests can often be circumvented by careful analysis of clinical data.

Unfamiliarity with spontaneous strokes in the young may motivate the perplexed clinician to subject the patient to a consecutive series of elaborate tests to uncover the elusive etiology. Syphilis and hypertension are easily and readily eliminated. Brain tumor, collagen disease, and congenital and acquired diseases of the vascular and hematologic systems are then sought after. The multiple tests necessary to investigate these various possibilities are usually negative. But the time consumed is often sufficient to permit spontaneous improvement. An erroneous diagnosis of multiple sclerosis is then often made by exclusion.

Most spontaneous (arterial) strokes in the healthy young are due to solitary atheromatous plaques similar to those found in older patients. Stress seems to precipitate the attack in some cases.

Development of a rational therapeutic program rests on accumulation and assessment of further data, especially on pathogenesis. The usefulness of anticoagulants in the treatment or prevention of a "stroke" requires further validation. Prognosis in these selected patients was generally good with no specific treatment. The indiscriminate use of anticoagulants without proper refinement of the heterogeneous diagnosis of "stroke" is haz-

ardous. Increased bleeding into a hemorrhage infarct is a particular danger

Further study of strokes in the healthy young would be particularly rewarding since the causative lesion can be studied in "pure culture," without contamination of the issue by the diffuse and multiple degenerative changes accompanying strokes in elderly patients.

Summario in Interlingua

Le occurrentia de apoplexia spontanee in juvene subjectos normotensive de apparentemente bon sanitate non es rar. Iste facto es illustrate per le presentation de 32 casos de apoplexia in subjectos de etates de inter cinque e medie e 44 annos. Le serie non include casos con morbo primari de character traumatic, neoplastic, infectiose, embolic, o altere. Esseva distinguite duo major gruppos etiologic secundo le causation per (1) thrombosis cerebro-venose o (2) thrombosis cerebro-arterial. Le secunde de iste gruppos includeva 16 casos, plures causate per thrombosis del arteria carotidic. Le diagnose de thrombosis del arteria carotidic es frequentemente possibile super le base de observation clinic, incluse un historia de declaration acute de mal de capite con hemiplegia contralateral e syndrome de Horner ipsilateral. Palpation del arteria carotidic e ophthalmodynamometria es utile technicas que merita un plus frequente empleo, sed illos non es infallibile. Arteriographia es frequentemente indispensabile, specialmente pro excluder aneurysma o tumor intracranial, sed tests que es dolorose, periculose, e innecessari pote esser evitate in multe casos per le analyse meticulose del datos clinic.

Non-familiaritate con le occurrentia de apoplexia in subjectos de juvene etates pote inducer le medico, qui se senti perplexe, a subjicer le patiente a un serie consecutive de complicate tests que visa a discoperir le elusive etiologia. Syphilis e hypertension es facile a eliminar. Postea, le possibilitate de tumor cerebral, de morbo de collageno, e de congenite o acquirite morbos del systemas vascular e hematologic es investigate. Le multiple tests, que es necessari pro investigar iste varie possibilitates, es usualmente negative, sed le tempore usate in illos es frequentemente satis extense pro permitter le supervenimento de un melioration spontanee. Alora un diagnose erronee de sclerosis multiple es frequentemente facite per exclusion.

Le majoritate del spontanee attaccos apoplectic in subjectos juvene in bon stato de sanitate es causate per solitari placas atheromatose, simile a illos trovate in patientes de etate plus avantiate. Il pare que stress precipita le attacco in certe casos.

Le disveloppamento de un programma rational de therapia depende del accumulation e evalutation de datos additional, specialmente de datos de importantia pathogenetic. Le utilitate de anticoagulantes in le tractamento o le prevention de attaccos apoplectic ha non ancora recipite un validation definitive. Le prognose in le seligite patientes del presente reporto esseva bon, in le absentia de un tractamento specific. Le uso indiscriminante de agentes anticoagulante, sin un appropriate raffinamento del heterogenee diagnose de apoplexia, es hasardose. Le augmentate sanguination a in un infarcimento hemorrhagic es un periculo particular.

Studios additional de apoplexia in juvene patientes in bon stato de sanitate esserea particularmente interessante, proque le lesion causative pote esser studiate in "cultura pur," i.e. sin le contamination del histos per le diffuse e multiple alterationes degeneratori que accompania attaccos apoplectic in patientes de etate plus avantiate.

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HEMATOLOGIC PROBLEMS ASSOCIATED WITH THE USE OF EXTRACORPOREAL CIRCULATION FOR CARDIOVASCULAR SURGERY *†

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Extracorporeal circulation maintained by an artificial heart-lung apparatus is now an essential and established procedure for certain types of cardiovascular surgery. With this new development has come a host of special blood problems that covers a wide spectrum of hematology from coagulation to blood banking technics.

Fortunately, a large number of these problems have been or are being solved, so that in the last two years the use of extracorporeal circulation has become relatively safe and is being employed in a large number of medical centers in this country and abroad.

Up to the present time, extracorporeal circulation is still limited as to the duration of safe perfusion, and very few successful clinical perfusions by-passing the heart and lungs have been carried out for longer than one or two hours. Perhaps the most important factors limiting its use are its effects, not only upon the formed elements of the blood, such as the platelets and red cells, but also on certain labile proteins of the plasma.

To appreciate more fully the effects of extracorporeal circulation upon the blood, it is important to consider the abnormal environment, foreign surfaces, and possible trauma inflicted by them in the extracorporeal circuit.

In most instances of cardiopulmonary by-pass, the blood leaves the patient through two large plastic catheters, one draining the inferior vena cava and the other draining the superior vena cava (figure 1). These two catheters may both be inserted through the right atrium or, one may in the case of inferior caval drainage be inserted via one of the femoral veins. These two venous outflow catheters then join before reaching the venous pump. With some systems, this venous blood from the cavae is collected by gravity drainage into a receptacle from whence it is pumped to the oxygenator. In other systems, the venous blood is pumped via the caval catheters directly to the oxygenator.

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In addition to this systemic venous blood, there is also the coronary sinus blood that drains into the operative field, plus an additional quantity from the lungs in those patients with well developed bronchial collateral circulation. This "loose" blood must be aspirated through some type of

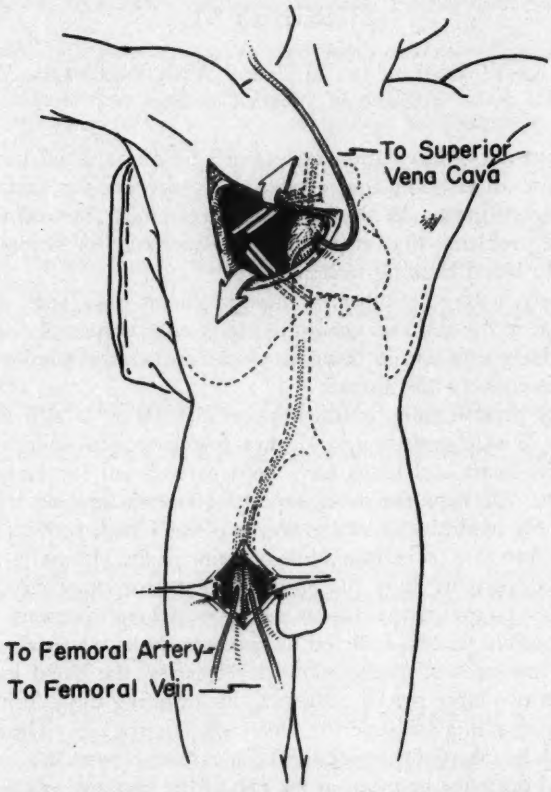

FIG. 1. Diagrammatic sketch showing one method of inserting the venous outflow and arterial inflow catheters into the patient. In this instance the superior vena cava is cannulated via the right auricular appendage and the inferior vena cava via the right femoral vein. The arterial inflow catheter is inserted into the right femoral artery.

sucker and returned to the extracorporeal circuit in order to avoid too great a blood loss from the system. Obviously, the blood which is sucked through this circuit to the heart lung machine is subject to the greatest trauma.

Perhaps the most important unit of the extracorporeal circuit is the oxygenator, of which there are three basic types: (1) filming, (2) bubbling, and (3) membrane (figure 2).

With the screen-type of filming oxygenator,[1,2] venous blood flows down stainless screens in a thin film while exposed to an atmosphere of pure oxy-

gen, or a mixture of high oxygen and low carbon dioxide. In the rotating-disc type of filming oxygenator,[3-5] the blood is lifted as a thin film on the turning disc surfaces into flowing oxygen as the blood moves along to the arterial outlet. In the bubbling type,[6] blood is oxygenated and the CO_2 removed as the blood is foamed upward on microbubbles of oxygen into a defoaming chamber containing a silicone defoaming agent. The antifoam compound * is thinly coated on the interior of the chamber, which usually contains various amounts of coarse stainless steel wool or plastic fibers to

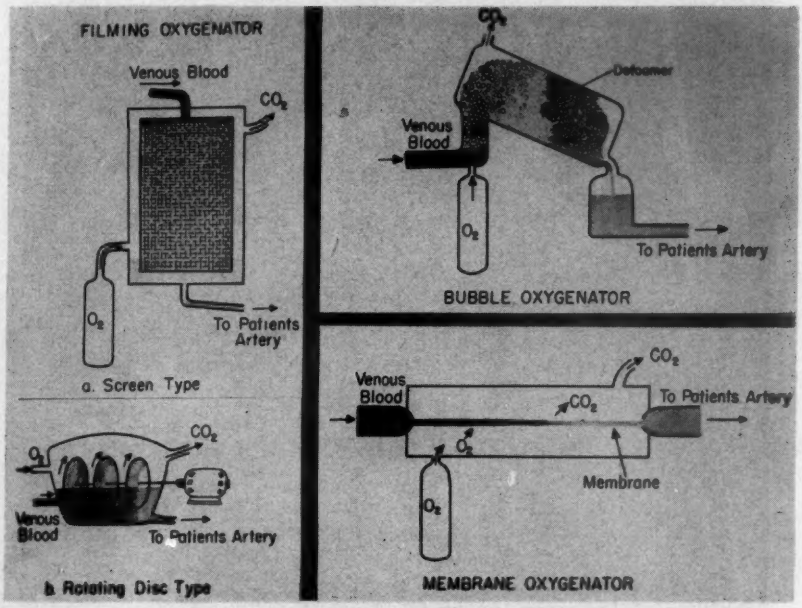

FIG. 2. Diagrammatic sketch showing the principle of operation of the three types of blood oxygenators in current clinical use.

aid in disrupting the bubbles. The third, and perhaps the most physiologic oxygenator in current use, is the membrane type[7] (figure 3). With this apparatus the blood is passed over a large surface area between exceedingly thin plastic membranes which are permeable to both oxygen and carbon dioxide.

After passing through the oxygenator and collecting in some type of reservoir, the blood is then pumped into one of the patient's systemic arteries, usually the femoral or left subclavian. The pumps that have been designed for propelling the blood through these circuits are even more numerous than are the various oxygenators. Some, like the DeBakey type (figure 3), compress elastic tubing by rotating rollers. The popular Sigmamotor pump

* Antifoam A manufactured by Dow Corning, Inc., Midland, Michigan.

(figure 4) propels the blood through elastic tubes which are compressed by the peristaltic action of multiple finger-like rods. Some pumps are occlusive, others are nonocclusive. Some have valves and automatic regulating mechanisms, but undoubtedly all inflict some degree of mechanical trauma to the

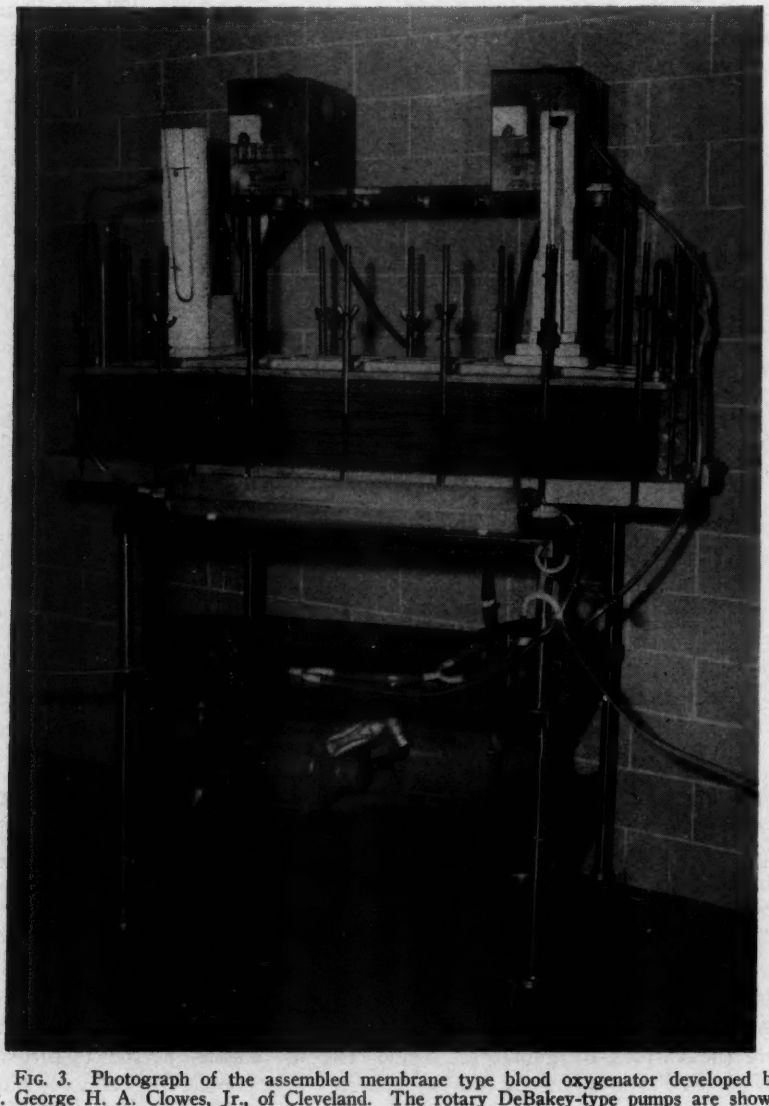

FIG. 3. Photograph of the assembled membrane type blood oxygenator developed by Dr. George H. A. Clowes, Jr., of Cleveland. The rotary DeBakey-type pumps are shown on the shelf below the oxygenator.—Courtesy Dr. Clowes.

blood, taking a varying toll of the cellular elements, particularly the platelets and red cells.

While most modern heart-lung machines have been designed to present the cleanest, smoothest nonwetting surfaces to the blood in its extracorporeal passage, practically every apparatus has a number of other foreign objects in the path of the blood. These include various electrodes and contacts for recording O_2 tension, pH and temperature. These same circuits may also include flowmeters, filters and blood heaters or coolers. Consequently, it is to be expected that this man-made heart-lung circulatory system would

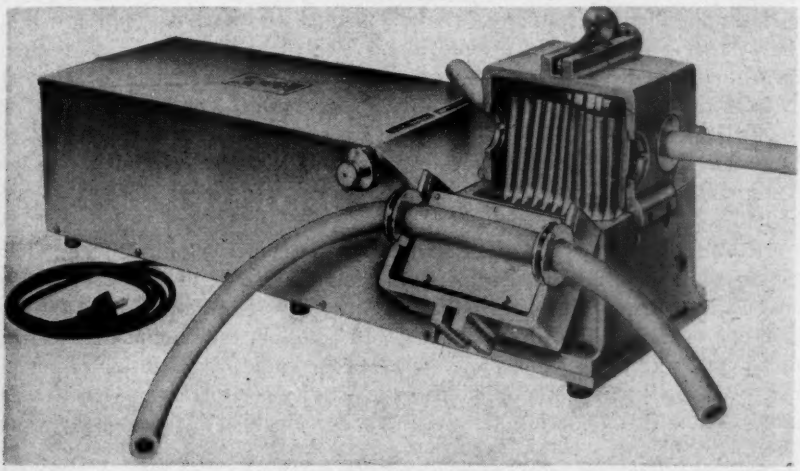

FIG. 4. Photograph of the Sigmamotor cross circulation pump model T-M2. The pumping action results when the cam operated fingers, shown exposed in the open left side pump head, press in sequence against flexible tubing. One pump head propels the venous blood to the oxygenator, the other pump head pumps the oxygenated blood into the patient and maintains the blood pressure during the by-pass.—Courtesy Sigmamotor Inc., Middleport, N. Y.

cause some deleterious changes in the blood flowing through it. Indeed, it seems remarkable that so few effects on the blood have been observed thus far.

Effects on the Coagulation Mechanism: Early in the experience with heart-lung machines there was considerable and frequent difficulty with clotting defects associated with excessive bleeding occurring after the perfusion period. While clotting defects still occur occasionally, this difficulty has been largely eliminated by more careful attention to hemostasis during surgery, more careful cleansing and preparation of the extracorporeal circuits, and improved apparatus resulting in less trauma to the blood. As with most problems of blood coagulation, there seems to be no general agreement as to the basis of the bleeding tendencies which do occur. A number of causes have been considered,[8-10] including (1) incomplete neutralization of

heparin (heparin rebound), (2) loss of platelets, (3) activation of fibrinolysins, (4) loss or denaturization of some essential clotting element, (5) activation of coagulation by trauma inflicted during the extracorporeal circuit, with consumption of essential clotting elements, (6) activation of some circulating anticoagulant, and (7) loss of capillary tone, etc.

In general, it can be stated that there is usually a drop in platelet count to one-half or one quarter or less of the pre-perfusion levels. This loss of platelets seems to depend considerably upon the presence or absence of pyrogens in the apparatus, the flow rate, the type of heart-lung machine employed, and the duration of perfusion. In addition to the possible loss on the foreign surfaces and the loss from direct trauma, any activation of coagulation within the system contributes to platelet loss. The thrombopenia is most often transitory, usually lasting only a few hours, but it may persist for as long as from two to four days postoperatively. However, it is rare at any time for the platelets to drop below 50,000 to 75,000 per mm^3, and no cases have been reported that exhibited clinical signs of thrombopenia, such as a positive Rumpel-Leede test, or petechiae, or where the hemorrhagic tendency could be laid solely to platelet deficiency.

In one of the few published studies on the hemorrhagic tendency after extracorporeal circulation, Osborn et al.[8] found evidence of activation of the coagulation process during perfusion which they felt was followed by exhaustion of essential clotting elements. In addition, they found that plasma fibrinolytic activity developed and increased the longer the duration of pumping. We too [11] have observed fibrinolytic activity post-perfusion, but in only one instance in our series has this been accompanied by a post-perfusion bleeding tendency.

More recently, Perkins, Osborn and Gerbode [10] have demonstrated an abnormality in prothrombin consumption after extracorporeal circulation. They found that immediately following those perfusions in which the blood was subject to the most trauma, prothrombin consumption was normal or excessively complete, but a few hours later the prothrombin consumption decreased, presumably after excessive thromboplastin liberated by the perfusion had been removed or neutralized. The concept of liberation of thromboplastin with consumption of essential clotting factors, particularly for the first stage of coagulation, is further supported by the recent work of Penick, Averette and Peters.[12] These investigators transfused normal dogs with blood which had been subjected in vitro to an artificial heart-lung circuit for varying periods of time. The dogs responded to transfusions of this blood with reactions similar to those produced by intravenous thromboplastin injection. Furthermore, the platelet and antihemophilic factor levels in these recipient dogs showed marked temporary decreases, again suggesting that a systemic type of coagulation had taken place, perhaps in response to activated thromboplastin in the pumped blood. In addition to the potential source of thromboplastin in plasma and platelets, Troup and Reed [13] have

reported evidence that red cells contain considerable thromboplastin, and it is not inconceivable that fragmented red cells disrupted in the heart-lung machine could be another source of this material. From all available evidence it would appear that the bleeding tendency may be due to more than one cause, and perhaps in most affected patients is the end result of multiple coagulation defects.

It seems certain that before cardiopulmonary by-pass can be utilized for extended periods, such as for acute heart failure, the hazard of postperfusion bleeding must be overcome. It is fortunate that most open heart surgery attempted at present can be accomplished within a relatively safe perfusion period before this complication develops.

Effects on White and Red Blood Cells: Most studies have shown that the white blood cell count drops moderately during perfusion, then rises to normal or above shortly after perfusion.[14] The greatest drop during perfusion occurs among the granulocytes, but whether this drop represents destruction of white cells or perhaps partial sequestration by the spleen has not been determined. No persistent postperfusion leukopenia has been reported.

A number of studies of hemolysis [14–16] occurring during perfusion have been made, and here again this has been found to be related to the apparatus employed, particularly the type of pump, the flow rate and duration of perfusion. There is no doubt that all artificial heart-lung machines give rise to some degree of hemolysis, and reported plasma hemoglobin levels have ranged from 20 to 200 mg.%. In addition to the mechanical hazards, the red cells may also be hemolyzed if overheated by improper or malfunctioning equipment employed to restore heat lost by the blood in the extracorporeal circuit. An efficient blood heat exchanger which employs a safe thermal gradient to overcome this latter hazard has recently been described.[17]

Some patients have been noted to develop a slight to moderate drop in hemoglobin and hematocrit by the seventh to the tenth postoperative day;[18] however, the fact that very few patients without unusual postoperative blood loss require transfusion in the postoperative period is evidence against latent red cell damage due to extracorporeal trauma.

Red cell survival studies of blood which has circulated through a pump oxygenator have revealed some interesting data, the interpretation of which is not entirely clear. It has been found that those red cells which survive the perfusion intact have a normal post-transfusion survival, at least for the first two to four weeks. However, there may be a random loss of donor cells remaining at that time which is gradual at first, then more rapid, until they have all but completely disappeared from the recipient's circulation.[19] This portion of the red cell survival curve assumes a sigmoid shape. At first we were unable to explain this delayed red cell loss, for the same heart-lung exposed blood would show this abnormal survival curve in one recipient and normal linear survival in another (figure 5). However, this abnormal

disappearance has not been observed when the exposed red cells were returned to the circulation of the donor.

In spite of the donor and recipient bloods being completely compatible according to elaborate serologic tests before transfusion, there were many facts—such as the S-shape of the abnormal disappearance curve following the initial three- to four-week period of normal survival—which indicated red cell destruction by recipient antibodies provoked by the transfused cells. This hypothesis would also account for the variable occurrence of abnormal survival in different recipients.

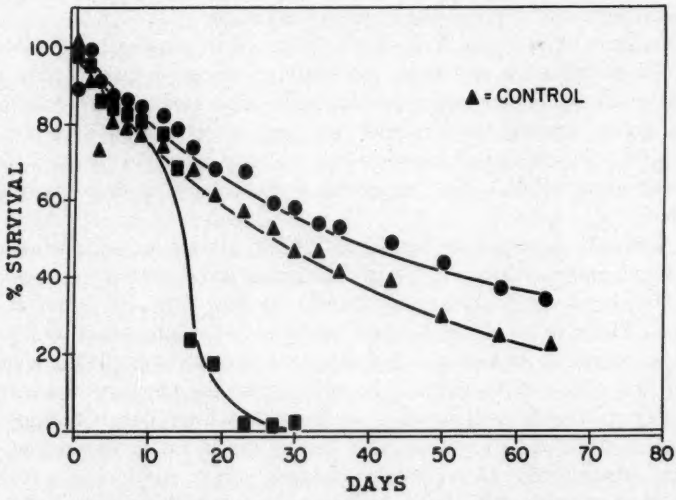

FIG. 5. Chromium-51 red cell in vivo survival curves of blood from the same donor exposed in vitro to an artificial heart-lung circuit for 15 minutes prior to transfusion into healthy compatible recipients. Control (▲) survival curve of aliquot of cells not exposed to artificial heart-lung. Note S-shaped disappearance curve of exposed cells after two weeks of normal survival in one recipient (■), and continuous normal survival of same exposed cells in another recipient (●). Points corrected for radioactive decay but not for elution of the isotope.

However, in only two of 27 recipients has any type of red cell antibody been detected by serologic tests. One recipient subject was found to have an anti-Kell antibody in his serum, and a second recipient, anti-C plus another red cell antibody, as yet unidentified. In both recipients these antibodies were demonstrable for the first time only after the rapid disappearance of the heart-lung exposed cells had occurred (three to four weeks post-transfusion).

The question arises whether this capability of provoking antibody response is more characteristic of red cells which have been exposed to a pump oxygenator than of nonexposed cells. The indirect tagged red cell method of demonstrating incompatible red cell antibodies undetectable by

serologic means has only recently been employed,[20] and so far no large series of single or multiple routine transfusions have been studied in this way. However, large numbers of red cell survival studies have been carried out in blood preservation experiments and, to our knowledge, this delayed S-shaped disappearance of supposedly compatible cells has been seen on only one or two occasions.[21] Yet in the small series of transfusions with blood circulated through a heart-lung machine, we have seen it in more than 20% of the recipients tested.

The true significance of these findings is not yet clear, but the question arises whether exposure to the pump oxygenator enhances in some way certain red cell antigens so that antibodies to them are provoked when these cells are transfused to certain susceptible recipients. Perhaps that fraction of mechanically hemolyzed red cells always present in artificial heart-lung exposed blood acts as a better stimulus for antibody production to certain of the lesser antigenic blood group factors in susceptible subjects than do intact red cells. The answers to these questions must await further study.

Special Blood Requirements for Extracorporeal Circulation: In addition to the effects on proteins and cellular elements, extracorporeal circulation has posed some special blood requirements of great importance to the heart surgeon, and these in turn have brought unusual problems to the blood banks.

Blood collected in heparin solution instead of the conventional sodium citrate, citric acid, dextrose mixture (ACD), usually begins to form small clots within 24 to 36 hours after collection. In addition, without glucose, proper buffering and addition of certain other salts, the post-transfusion survival of the red cells is sharply limited and platelets rapidly disappear.

Consequently, it is customary with most blood banks to procure this blood fresh within 24 hours before operation. To avoid wastage and yet insure the necessary quantity of compatible blood, blood banks and families have been burdened with planning, well in advance of operation, the recruitment, typing and crossmatching of donors, or the cost and problems of obtaining professional donors of known type. In cases with rare blood groups it is frequently difficult to meet the blood needs under these conditions.

These problems stem from the absolute need for fresh heparinized blood of low dilution and of near-normal pH and electrolyte composition. For the surgical cardiac patient the importance of avoiding excess sodium or extracellular potassium in the priming donor blood is obvious. Low pH of the donor blood must be avoided to prevent any further reduction in pH of the patient's blood below that consequent to the operation and extracorporeal circulation. Not so well appreciated, yet equally important from the cardiac standpoint, is the necessity of maintaining a near-normal level of ionized calcium during and immediately after the critical cardiopulmonary by-pass portion of the operation.

Ringer in 1883 [22] first pointed out the essential need of calcium in main-

taining normal cardiac function. Since that time much has been learned concerning the effects of calcium and its interaction with other cations, particularly on the electrocardiogram.[23-28] Perhaps less appreciated is the inotropic action of calcium and the marked depression of cardiac contractility and cardiac output that accompanies low levels of ionized calcium.

Garb [29] has shown a complete loss of contractility with maintenance of a regular electrogram in the presence of low calcium when the papillary muscle of the cat's heart was bathed in an otherwise balanced salt solution. Hubbard, Neis and Barmore [30] have described a clinical experience of acute heart failure during heart surgery following rapid pressure infusion of citrated blood. In addition to the classic electrocardiographic changes of prolongation of the Q-T interval and ST segment, these observers noted a progressive fall in the arterial and right ventricular pressures, poor cardiac contractility and acute cardiac dilatation. These changes quickly reverted to normal on injection of calcium chloride. We [11] and others [31] have observed similar changes while perfusing dogs intra-arterially with citrated or ion exchange resin-treated blood with low or absent ionized calcium content.

TABLE 1

Ed-glu-gate Mg Solution

Na_3H_2EDTA, 0.080 M	3.44 ml.
Na_3HEDTA, 0.080 M	10.31 ml.
Sodium gluconate 0.167 M	10.00 ml.
Magnesium chloride 0.10 M	1.5 ml.
Glucose 1.5 g as 50% solution	3.0 ml.
Water q.s. ad	30.0 ml.

Osmolarity 550 mOsm/L.

To meet these special blood requirements and at the same time attempt to solve some of the practical blood bank problems they create, we have been studying a new anticoagulant-preservative mixture for donor blood intended for use during the extracorporeal by-pass.

This solution,* which we have termed Ed-glu-gate Magnesium, contains sodium Edathamil, sodium gluconate, glucose and magnesium chloride composed as shown in table 1. The sodium Edathamil replaces the usual sodium citrate as the initial anticoagulant. The small amount of sodium gluconate in addition to the glucose has been found to enhance preservation of the red cells should the blood not be used for extracorporeal circulation but be stored instead for a longer period for routine use. The small amount of magnesium chloride is added to inhibit inactivation of Factor V by the Edathamil.[33]

Blood for extracorporeal circulation may be stored in this mixture for from three to five days before operation with excellent platelet preservation. When during the operative procedure it has been definitely decided that extracorporeal circulation will be employed, the blood is taken from the refrigerator and 15 mg. of heparin are added to each 500 c.c. unit. After

* Details of preparation of this anticoagulant-preservative solution and results of its use are the subject of another report.[32]

mixing, calcium chloride solution containing 1.1 mM of Ca^{++} is added. The sharp chemical equivalence relationships between Ca^{++}, Mg^{++} and the Edathamil are employed in this conversion to restore the plasma Ca^{++} and Mg^{++} concentrations and ratios to normal levels.

At this point the heparinized and calcium reconstituted blood is added to the heart-lung machine. If the blood is not used for extracorporeal circulation (not heparinized or reconstituted), it may be stored for routine transfusion for at least two weeks, with post-transfusion red cell survival equal to that provided by ACD preservative. Thus, for this purpose, the hazard of having to reënter the blood container with a preservative (as with originally heparinized blood) is avoided.

Thus far our limited experience employing this anticoagulant-preservative mixture for extracorporeal circulation has been most successful. However, its final acceptance for this purpose must await further clinical trial.

Summary

A number of the hematologic problems associated with extracorporeal circulation for open heart surgery have been discussed.

The post-perfusion bleeding tendency, while occurring less frequently as more experience is gained and less traumatic heart-lung machines are developed, is still a major factor limiting the duration of safe cardiopulmonary by-pass. A number of causes of the postoperative bleeding tendencies have been considered and, while multiple factors may be involved, presently available evidence implicates activation of systemic coagulation through liberation of thromboplastic substances in the extracorporeal heart-lung circuit.

The blood platelets are consistently decreased during and following most extracorporeal perfusions. Though usually temporary, the thrombocytopenia may persist for from two to four days. Unless the perfusion is unduly prolonged, the platelet level rarely drops to hemorrhagic levels. White cell counts are also temporarily depressed. Mechanical destruction of red blood cells during perfusion, though occurring to some degree with all types of heart-lung machines, is no longer a serious problem with the most modern pumps and oxygenators. Ordinarily, those red cells which survive the perfusion period intact exhibit normal in vivo survival for at least two to three weeks, and sometimes longer. Evidence is presented that certain susceptible recipients of donor blood which has been exposed to an artificial heart-lung circuit may destroy this blood, presumably through antibody formation to certain lesser antigenic blood group factors, after permitting varying periods of initial normal red cell survival. Whether this indicates that exposure of blood to an extracorporeal circuit enhances the antigenicity of certain blood group factors, or whether this phenomenon occurs with

equal frequency among recipients of large transfusions of unexposed blood, is yet to be determined.

The importance of maintaining low blood dilution, near-normal pH and normal electrolyte pattern, particularly of ionized calcium, of the donor blood is emphasized. These special blood requirements for extracorporeal circulation present difficult problems for blood banks. A possible solution to some of these problems is suggested through the use of a new anticoagulant-preservative mixture now under current study.

Summario in Interlingua

Le technica del circulation extracorporee, hodie in uso extense in certe typos de chirurgia cardiovascular, ha sublevate un numero de problemas hematologic que es de interesse pro le hematologo mesme e pro le chirurgo e le bancas de sanguine.

Durante que defectos postoperatori in le coagulation del sanguine esseva incontrate frequentemente durante le disveloppamento initial del circulation extracorporee, meliorationes in le machinas de corde-pulmon—con plus attention prestate al detersion del apparatura e al prevention de excessive grados de trauma in le sanguine—ha resultate in le elimination de iste complication. Tamen, tendentias sanguinatori occurre ancora in casos sporadic, causate le plus frequentemente per (1) neutralisation incomplete de heparina con protamina (heparina re-ligate), (2) activation de fibrinolysina, o (3) consumption de essential factores de coagulation, forsan in consequentia de un activation del mechanismo coagulatori durante le passage extracorporee. In le majoritate del casos studiate, le tendentia sanguinatori esseva le producto de plure defectos in combination.

Se nota usualmente un reduction de numerationes plachettal e leucocytic usque a inter un medietate e un quarto del nivello pre-perfusional. Le basse numeration plachettal es transitori sed pote persister durante inter un e quatro dies. Hemolyse intravascular ha cessate representar un serie problema, ben que moderne machinas de corde-pulmon es in uso pro perfusiones de un duration de un o mesmo duo horas. Le superviventia post-perfusional de erythrocytos es normal in le majoritate del casos. Tamen, un certe grado de tardive perdita de erythrocytos ab donatores ha essite notate in certe recipientes qui disveloppa anticorpore contra un o plures del antigenos del cellulas de donation. Si o non le frequentia de iste phenomeno es plus alte quando le cellulas de donation es subjicite al action de un pumpa-oxygenator remane incerte. In le majoritate del casos, le anticorpores in question non es detegibile per le usual methodos serologic.

Le uso de fresc sanguine heparinisate es essential in le circulation extracorporee. Isto ha sublevate un numero de difficile problemas ab le puncto de vista del bancas de sanguine. In un effortio de solver iste problemas, un nove mixtura anticoagulante-preservatori pro sanguine de donation es sub investigation. Illo contine acido ethylenediaminotetraacetic, gluconato de natrium, glucosa, e chloruro de magnesium. On spera que iste nove mixtura va permitter le preservation de sanguine de donation durante quatro a sex dies ante su uso in un circulation extracorporee e durante usque a 20 dies ante su uso in un transfusion routinari.

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HYPERTENSIVE CEREBROVASCULAR DISEASE: A CLINICAL AND PATHOLOGIC REVIEW OF 100 CASES *

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AMONG the most challenging and important diseases of man with regard to the incidence of morbidity and mortality is degenerative vascular disease. Vascular degeneration due to hypertension has been extensively studied [1, 2] from the clinical, pathologic and therapeutic aspects. Pickering [2] has recently made a comprehensive review of the present state of our knowledge, and in a more specialized study Clarke and Murphy [3] reviewed a series of cases with neurologic manifestations of malignant hypertension, their cases having been selected with regard to nervous system involvement. The present study was instituted to determine the natural history of hypertension causing death, with particular reference to the nature and incidence of clinical involvement of the central nervous system. It is realized, of course, that the influences of hypertension are complex, since vascular changes in the kidneys, heart, etc., produce indirect metabolic actions which may become superimposed upon the direct effects of cerebrovascular degeneration.

METHOD AND MATERIAL

This study of hypertensive cerebrovascular disease was based upon a series of 100 fatal cases selected from the records of the Toronto General Hospital from 1933 to 1956, each case having had indisputable evidence of high blood pressure and a detailed autopsy examination. Since it was desired to evaluate clinical symptoms, cases without good clinical records were excluded.

The cases were not specifically selected from the standpoint of their neurologic interest, but included those with other than the neurologic sequelae of hypertension. As far as was possible, cases were not included in this series that had other serious disease, particularly diabetes and rheumatic heart disease, which produce degenerative vascular disease or modify in a significant way the natural history of hypertension. Hemorrhage due to rupture of a saccular aneurysm was also excluded, since it may occur in the absence of hypertension. However, the hypertension was not exclusively of the "essential" variety, but included cases with renal disease as their cause.

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There were no instances of pheochromocytoma, Cushing's disease, coarctation of the aorta or other unusual causes in this series. Hypotensive agents had been administered in a few instances but for only a relatively short period preterminally. Blood pressures recorded during their administration were disregarded for the purpose of this study.

TABLE 1

Individual Average Blood Pressures, 100 Cases of Hypertension

1	207/120	34	230/140	67	224/147
2	220/127	35	234/136	68	209/129
3	218/113	36	203/131	69	220/143
4	196/92*	37	235/105	70	203/113
5	195/110	38	246/140	71	247/160
6	191/101	39	235/100	72	190/133
7	267/155	40	275/115	73	241/105
8	185/130	41	222/131	74	245/148
9	193/111	42	250/107	75	220/95
10	218/129	43	213/153	76	230/142
11	220/160	44	247/105	77	210/130
12	196/106	45	253/135	78	195/113
13	253/128	46	202/127	79	213/120
14	212/140	47	244/139	80	220/120
15	209/129	48	215/110	81	227/129
16	240/130	49	229/124	82	230/134
17	195/131	50	216/116	83	245/137
18	178/110*	51	245/130	84	241/157
19	205/105	52	218/135	85	224/142
20	188/109	53	200/129	86	230/118
21	197/118	54	244/142	87	215/137
22	190/115	55	236/90	88	240/150
23	180/123	56	202/135	89	234/171
24	232/103	57	227/120	90	202/102
25	223/121	58	215/130	91	207/131
26	208/113	59	194/106	92	204/109
27	246/142	60	215/91	93	238/145
28	240/100	61	220/140	94	205/121
29	213/120	62	247/150	95	256/162†
30	209/130	63	254/129	96	200/136
31	235/132	64	233/137	97	227/125
32	232/146	65	230/140	98	197/122
33	229/156	66	192/120	99	200/100
				100	213/142

* Lowest average individual blood pressure.
† Highest average individual blood pressure.

Blood pressures may vary considerably, particularly in the earlier or benign phase of hypertension.[1] It is recognized that complete rest in a hypertensive subject may induce a return of blood pressure to even normotensive levels and that, despite the repeated finding of hypertension, there may be no evidence of deterioration. However, a persistent elevation of blood pressure may develop, with ensuing degenerative vascular changes producing a further decrease in variability. Thus, in a series such as this, where the subjects have succumbed to the degenerative vascular changes of hypertension, blood pressure recordings within one to two years preceding death probably provide a more reliable indication of the actual state of the

blood pressure than do the recordings in those who survive many years, apparently without deterioration. With this in mind, as many reliable reports as possible were taken from each case of the series within a few years preceding demise, an average for each was obtained, and the mean pressure for the entire series was then determined. An analysis of cases with regard to signs and symptoms could therefore be better appreciated when the indi-

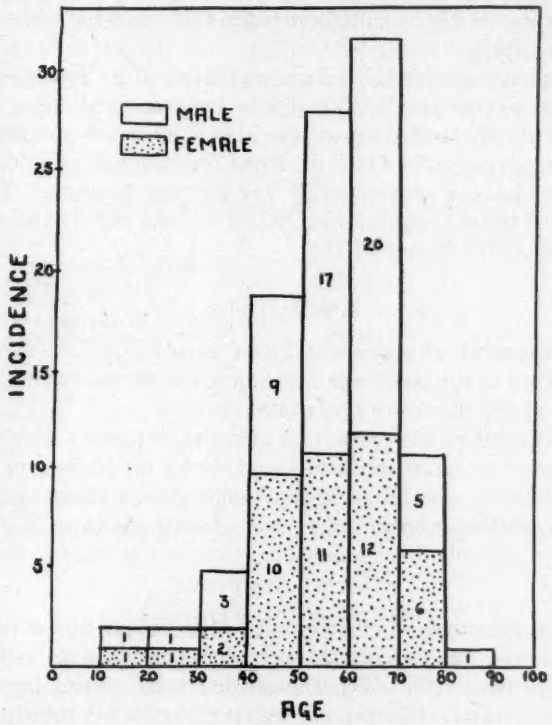

FIG. 1.

vidual average blood pressure was compared with the series average. They also provided numerical evidence of benign or severe hypertension, with the series average being taken as the reference point (table 1).

The average duration of hypertension or the length of time during which the patients had had recognized high blood pressure was slightly over seven years (7.25 years). The period of time during which a hospital record of blood pressure was kept is generally much shorter, usually within the last few years, and particularly within the year or so preceding demise. As noted, it was essentially in this period that the average was obtained. The major problem in such an analysis is that there will be a dearth of reliable records in a number of cases (12 of the series of 100 had only a single

record). However, the majority had several records, although the limitations are apparent, for even 10 or so blood pressure recordings do not permit a critical analysis.

The average blood pressure recording for the entire series was 220.37 systolic and 126.61 diastolic, or approximately 220/126 mm. of Hg. The standard deviation for the systolic pressure was 20.16, and for the diastolic, 17.36. The lowest individual (average) blood pressure of the entire series was 196/92 mm. of Hg, the highest individual (average) blood pressure, 256/162 mm. of Hg.

A maximal average blood pressure was obtained by averaging the maximal recording of each case. Although of little practical value, it provided a reference with which to compare the individual blood pressures of those with severe hypertension in which the blood pressure was unstable and therefore tended to have a comparatively low average pressure. The average of the maximal blood pressures was 243.35 systolic and 138.65 diastolic, or approximately 243/138 mm. of Hg.

Age and Sex

The total number of males was 57, of females, 43; the average age at the time of death of the males was 56.1 years, and of the females, 55.4 years. The average age of the entire series is 55.8 years.

Figure 1 illustrates the proportion of males to females with reference to age groups taken in terms of decades and shows the highest morbidity and mortality in hypertension in the 50- to 70-age span; a sharper rise and probably a higher relative incidence of males to females occur in this group.

Initial Symptoms

The initial symptom—or that symptom the patient first experienced and most often caused him to visit his physician—provided an estimate of the period of hypertension in which clinical deterioration had begun from the effects of the disease. However, it was not always his principal complaint thereafter, and, similarly, death may have been due to a cause concerning which he had had no previous symptoms. In some of the cases this symptom was perhaps unrelated to the hypertension, but the subsequent history usually substantiated its relationship, and when there was doubt concerning a particular symptom it was disregarded. The incidence and duration of initial symptoms are shown in table 2.

Shortness of breath on effort was the most frequent of the initial symptoms: the average period of four and a half years provides at least an approximate estimate of life expectancy, although the time of onset was perhaps only vaguely approximate in many cases, and occasionally preceded death by 10 or more years. All but a few with this initial symptom developed congestive failure (a small number had evidence of renal failure), but the

eventual cause of death in almost a third (14 cases) was a cerebral vascular accident. Of those who had a stroke (16 cases) as the initial manifestation of hypertension, three quarters died of a stroke (12 cases); thus those with a stroke as the first manifestation most often died of a cerebrovascular accident. Two of those dying of strokes (cerebral hemorrhage) had no previous history of illness related to hypertension.

As to the remaining initial symptoms, brief mention should be made of a few important features. The seven patients recorded as complaining of acute shortness of breath and anginoid pain were diagnosed as having coronary occlusion. Five of these developed congestive failure. Nocturia was a symptom which in males was considered only if prostatism could be excluded; two of the three males with nocturia had uremia, and one had

TABLE 2

Initial Symptoms of Deterioration in Hypertension

Initial Symptom	Incidence	Average Duration of Life
Shortness of breath (effort)	46%	4.4 years
"Stroke"	16%	3 years
Headache	14%	6.0 years
Anginoid pain and shortness of breath (transitory)	7%	2.4 years
Fatigue and weakness	7%	3 years
Nocturia and frequency	4%	3 years
Failing vision	3%	less than 1 year
"Blackouts"	1%	1 year
Palpitation	1%	3.5 years
Dizziness	1%	2 years

evidence of moderate renal damage without uremia. While dizziness and palpitation were not infrequent in association with other symptoms at onset, they occurred initially as the principal symptom in only two.

CEREBROVASCULAR ACCIDENTS

Cerebrovascular accidents are considered here as (a) those due to vascular insufficiency [4, 5, 7] or occlusion, and (b) those due to hemorrhage. Eighty-five per cent of the entire series had cerebral lesions due to hemorrhage or softening found at autopsy. In one quarter of these (21 cases) small softenings were found at autopsy without history of any clinical incidents or focal neurologic findings; most of those with a history of strokes had, in addition to the causative lesions, others which could not be correlated with the clinical history. Rosenberg [6] reported multiple softenings of 0.5 cm. or less in size in 12 of a series of 17 cases with hypertension. Admittedly, many in this series were of such small size (1 to 2 mm.) and location as to make it understandable that their presence in life would be undetected, but others were of a size (1 to 2 cm.), number or location that one would be led to expect more focal disability. Some showed intellectual deterioration, which will be discussed later. The autopsy material was not examined in minute detail, and therefore extremely small softenings and hemorrhages

may have been present more often than our figure of 85% would indicate. It is perhaps worth while to emphasize that in hypertension considerable damage to the brain may exist, particularly in the form of numerous miliary softenings, without evidence in the history or on clinical examination. This is apt to be the case with lesions confined to the cortex, but may occur with lesions in the subcortical white matter or brain stem.

I. Vascular Insufficiency or Occlusion. Forty-seven per cent (47 cases) of the whole series had a history of strokes which were considered to be due to vascular insufficiency or occlusion, an incidence much higher than that previously reported.[3] Almost half (22 cases) had a history of more than one ischemic episode. Hemiplegia or hemiparesis was the most frequent manifestation, but occasionally the signs were limited to monoplegia, speech defect, or transient dizziness and cranial nerve involvement, etc. The occurrence of cranial nerve palsies in hypertensive vascular disease has been emphasized by Griffiths.[9] Clinical differentiation between cerebral hemorrhage and cerebral thrombosis was occasionally difficult, although, as observed by Aring and Merritt,[8] there were often clinical features which suggested the diagnosis, later confirmed at autopsy. A notable exception to this was found with regard to nonfatal cerebral hemorrhages (vide infra).

The sex incidence showed females to males affected in a proportion of 28 cases to 19. Ages extended over a wide range, from 27 to 76 years, with an average age of 58, only slightly above the mean age of 56 for the entire series. The symptoms accompanying vascular insufficiency and occlusion are well recognized and so are not discussed here.

Terminal vascular occlusion which was largely or entirely responsible for death was found in 11 cases, these occurring in the carotid supply in seven and in the basilar distribution in four. Associated conditions, such as congestive failure or pneumonia, were contributing factors in a few. Fourteen of the 47 patients died of brain hemorrhage. It has been postulated [10] that massive hemorrhage may occur into a previous softening, and it is therefore of some interest that only seven of the 14 had the previous stroke on the same side as the terminal hemorrhage.

II. Brain Hemorrhage Causing Death. In 31% (31 cases) of the entire series death was due to a large intracranial hemorrhage. This is a higher incidence than has been reported in the literature (Jaffe,[11] 7.2%; Clarke and Murphy,[3] 14.3%; Rosenberg,[6] 24%). The range of age extended from 33 to 71 years, with an average age of 51, slightly less than the mean age of 56 for the entire series. The sex incidence was equal. The individual average blood pressures were not unusual, since they fell to either side of the mean for the entire series; however, maximal readings tended in the majority to be higher than in those not dying of intracranial hemorrhage. Five of the seven cases dying of pontine hemorrhage had individual average pressures above the average pressure of the entire series, which is of interest in view of Epstein's [12] claim that pontine hemorrhage was more com-

mon in those with the more severe forms of hypertension. About three-fifths of the patients with cerebral hemorrhage died within a day, although survival for 12 days occurred in one case, and several survived for from three to five days.

Eighteen cases, or well over half of the total of 31 cases of fatal hemorrhage, had had previous strokes. Fourteen of these had strokes which were considered, clinically and pathologically, to have been due to vascular insufficiency or occlusion. Six were found to have had strokes due to pathologically proved nonfatal hemorrhage (vide infra). Small softenings, not reflected clinically, were found at autopsy in several instances. Thus there was evidence of moderately severe cerebrovascular degeneration, as indicated by extensive brain damage, apart from the gross and histopathologic changes in the vessels.

(a) *Symptoms of Onset.* Three principal sites of hemorrhage were found: the cerebrum, pons and cerebellum (table 3). The anatomic incidence of cerebral hemorrhage corresponds approximately to that reported in the literature, although the incidence of pontine hemorrhage as recorded

TABLE 3

Fatal Brain Hemorrhage

Location	Incidence
Cerebral	23 cases (74%)
Left hemisphere	15 cases (48%)
Right hemisphere	8 cases (26%)
Pontine	7 cases (23%)
Cerebellar	1 case (3%)

here is slightly higher.[3, 5, 13] The majority of cases of intracerebral hemorrhage occurred in the region of the external or internal capsule and the thalamus. The cerebrum is discussed without reference to lateralization, except with regard to speech, since, apart from this, the essential features were the same.

(1) *Cerebrum.* There are several studies [2, 3, 14] on the clinical features associated with cerebral hemorrhage. Aring and Merritt,[3] in their report on the clinical characteristics of onset of cerebral hemorrhage, found an incidence of signs which, compared with their series total, is in accord with our experience. In their series an immediate onset of coma occurred in half of the 116 cases. Headache was a complaint in 26 of their cases (63.4% of the 41 cases in which this fact was mentioned), and convulsions occurred in eight cases (14.8% of the 54 cases in which this point was noted). The symptoms of onset of intracerebral hemorrhage in the present series are shown in table 4, and include 23 cases of fatal and four of nonfatal hemorrhage in which a good clinical record was available.

The incidence of symptoms, in particular headache, is low, since over half of the cases were almost immediately rendered unconscious or speechless. Numbness and tingling were encountered in a case of hemorrhage

into the posterior limb of the internal capsule with survival, and would seem an interesting localizing sign. The symptoms of onset in some cases occurred in combination, such as headache with numbness and tingling; in a few, nausea and vomiting preceded the onset of coma. Unconsciousness in fatal cerebral hemorrhage usually occurred within a matter of minutes, although very occasionally in an hour or so. In some instances there was temporary improvement in the level of consciousness and then a return to a progressively deepening coma. Paralysis appeared immediately following the prodromata in the instances where it did not appear first.

(2) *Pons.* The cases where there was primary hemorrhage into the midbrain showed the pons to be affected also. Thus, midbrain and pontine hemorrhages are grouped under the single heading of pons, a total of seven cases. All instances of pontine hemorrhage appeared to be primary and not secondary to increased intracranial pressure. In four of the seven cases

TABLE 4

Initial Symptoms of Cerebral Hemorrhage

Symptoms*	Incidence (27 cases)	
Sudden unconsciousness	12 cases	(44%)
Headache	7 cases	(26%)
Disorder of speech	5 cases	(18.5%)
Aphasia	3 cases	
Dysphasia	1 case	
Slurring	1 case	
Desire to void or defecate	3 cases	(11%)
Unilateral numbness and tingling	3 cases	(11%)
Seizure (focal)	2 cases	(7%)
Dizziness	1 case	(4%)

* Hemiparesis and paralysis were associated or followed rapidly in all instances.

the onset occurred with hemiplegia, coma supervening within several minutes. The symptoms initiating or associated with the hemiplegia were tingling of an arm, anarthria, dysarthria and weakness of a hand. The remaining three cases had an immediate onset of coma.

(3) *Cerebellar Hemorrhage.* Hyland and Levy[15] in a series of 30 verified cases of cerebellar hemorrhage, half of which occurred in association with hypertension, observed severe head pain, usually suboccipital (17 cases), vomiting (11 cases), mental confusion (seven cases), and "dizziness" (five cases), as the principal symptoms of onset, with collapse and unconsciousness occurring initially in only two. In the present series there was only one case of massive cerebellar hemorrhage. The symptoms began with sudden giddiness and confusion, followed by recovery, and in a few hours relapse into coma. The clinical and pathologic picture was complicated by a thalamic infarction occurring at the time of the cerebellar hemorrhage, the embolic nature of this being suggested by the almost coincidental infarction of the intestine and kidney, although a source for embolism was not found.

TABLE 5

Nonfatal Cerebral Hemorrhage

Location	Incidence
Internal capsule	3 cases (30%)
Occipital lobe	2 cases (20%)
External capsule	2 cases (20%)
Thalamus	2 cases (20%)
Temporal lobe	1 case (10%)

(b) *Cardiac and Renal Failure.* The occurrence of concomitant renal and cardiac failure with intracranial hemorrhage indicated a severe form of hypertension. In three of the 31 cases, renal and cardiac failure was present and moderately advanced, the individual average blood pressures being above the mean pressure of the entire series in all three (mean, 220/126 mm. of Hg). Severe hypertension was also present in the group of seven cases of frank congestive failure, the blood pressure in each being in the upper range of the series. A few cases with evidence of very early

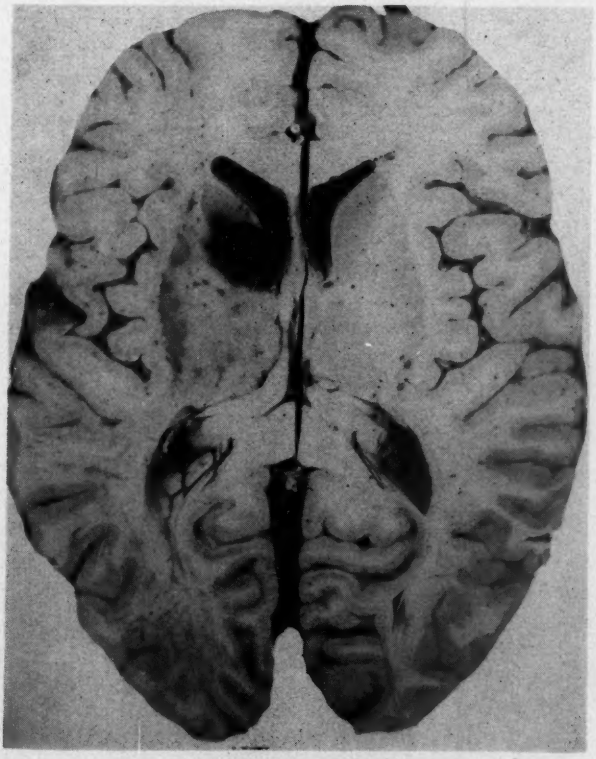

FIG. 2. (J. S.) Three month old, nonfatal hemorrhage into the left caudate nucleus and internal capsule, with slight intraventricular extension.

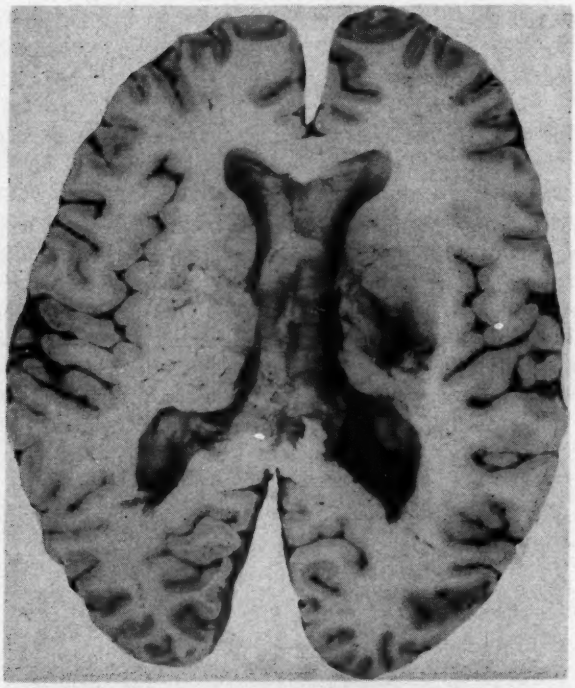

FIG. 3. (R. W.) Seven week old, nonfatal hemorrhage into the posterior limb of the right internal capsule, with intraventricular rupture.

cardiac failure also had severe hypertension, and it was evident that, had many of the patients not succumbed to brain hemorrhage, they would most likely have died of congestive heart failure with, in some cases, concomitant renal failure.

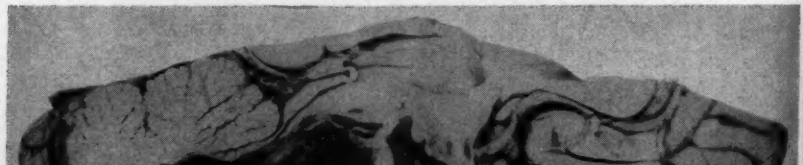

FIG. 4. (R. W., same case as fig. 2.) Fatal pontine hemorrhage occurring seven weeks after nonfatal right cerebral hemorrhage.

III. Brain Hemorrhage Not Causing Death. Brain hemorrhages which were compatible with survival were considered in two groups, dependent upon the size of the hemorrhage: (a) a moderate sized (1 to 3.5 cm.), single, symptomatic lesion, which we have designated as a "nonfatal brain hemorrhage"; (b) minute (miliary sized), often multiple and usually asymptomatic hemorrhage.

(a) *Nonfatal Brain Hemorrhage.* Ten cases (10%) were discovered to have had an intracerebral hemorrhage of a size sufficient to impair consciousness or motor and sensory function without a fatal outcome. The sites and incidence of these nonfatal hemorrhages are recorded in table 5. That these may have been the result of hemorrhage into a previous softening has already been discussed, but, if so, the extent of the hemorrhage was such as to obliterate any recognition of softening. The hemorrhages ranged from 1 to 3.5 cm. in diameter, and in half (five cases) their location resulted in intraventricular extension of bleeding (figure 2).

TABLE 6

Nonfatal Cerebral Hemorrhage

Case	Initial Hemorrhage	Interval	Cause of Death
R. W.	Post limb R. int. cap.	7 weeks	Pontine hemorrhage
J. S.	L. caudate and int. cap.	3 months	Hypoglycemia
C. L.	R. internal capsule	3 months	Pontine hemorrhage
H. C.	R. occipital lobe	2 months	L. parietal hemorrhage
C. B.	R. occipital lobe	6 weeks	Uremia
W. S.	L. external capsule	"old"	Congestive failure
F. N.	R. external capsule	8 months	L. basal ganglia hemorrhage
M. C.	L. thalamus	1½ years	L. external capsule hemorrhage
G. B.	R. thalamus	3 years	L. thalamus hemorrhage
F. W.	R. temporal lobe	2 months	Coronary thrombosis

Consciousness tended to be temporarily lost in the cases where hemorrhage occurred into the thalamus or internal capsule, whereas it tended not to be seriously affected in the cases of external capsule, temporal and occipital lobe hemorrhage. In both, the motor and/or sensory disturbances were of fairly sudden onset and often quite marked. Two of the 10 cases improved temporarily but did not do well subsequently, bleeding having continued to occur into the ventricular system, with symptoms of headache, drowsiness and vomiting; death occurred in seven to eight weeks due to massive hemorrhage elsewhere in the brain. In one of these (figures 3 and 4) the terminal hemorrhage was massive into the pons, and it could be argued [16] that this was the direct consequence of the supratentorial cerebral hemorrhage. Although there was little evidence of tentorial herniation, the significance of contributing factors, including angulation of the brainstem due to cerebral edema, is difficult to define in the malignant phase of hypertension. The other case (H. C.) had a terminal hemorrhage into the opposite hemisphere.

The ultimate cause of death in nonfatal hemorrhage is shown in table 6. No case of hemorrhage into the pons of comparable size with recovery was found in this series. The nonfatal hemorrhages ranged in age from six weeks to three years, with half occurring within three months of death. Since six of the 10 cases died of cerebral hemorrhage occurring elsewhere in the brain, it would appear that, in view of the tendency to further hemorrhage, and the often short period preceding recurrence, there were very

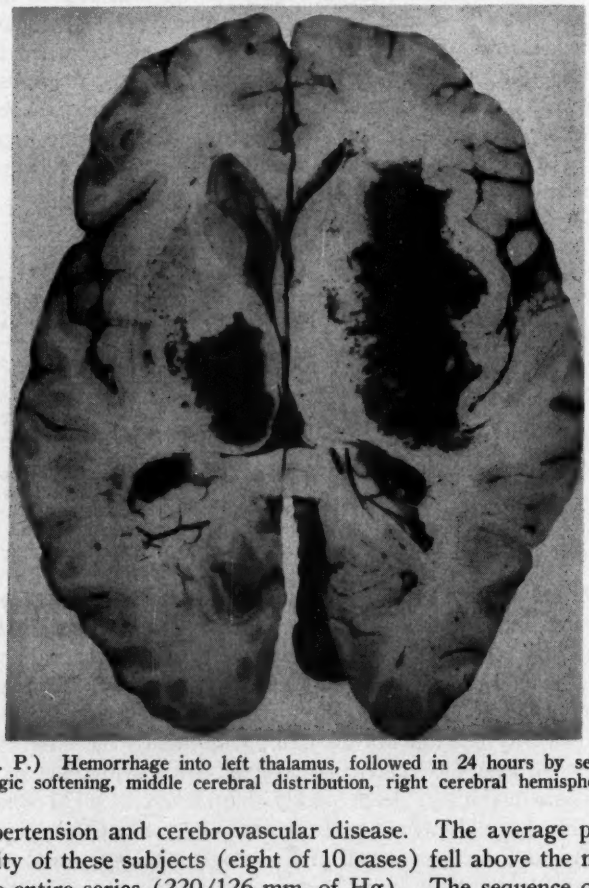

FIG. 5. (M. P.) Hemorrhage into left thalamus, followed in 24 hours by severe hemorrhagic softening, middle cerebral distribution, right cerebral hemisphere.

severe hypertension and cerebrovascular disease. The average pressure in the majority of these subjects (eight of 10 cases) fell above the mean pressure of the entire series (220/126 mm. of Hg). The sequence of vascular accidents can be swift, as occurred in one case, not included in this group (figure 5), in which a subject with a left thalamic hemorrhage, accompanied by one or two hours of unconsciousness, died of a right cerebral hemorrhagic softening which occurred 24 hours later.

Because of the tendency to higher blood pressures in this group, the cardiac and renal functions were reviewed. All gave evidence clinically

of cardiac impairment, although only three had frank congestive failure, one of which had concomitant uremia. One other case had advanced renal failure with uremia, while a few had a relatively slight elevation of the nonprotein nitrogen.

(b) *Minute Brain Hemorrhage.* Rosenberg [6] has reported the fairly frequent finding of minute brain hemorrhage in hypertension. In this series minute brain hemorrhages occurred in well over a quarter of the 100 cases. Linear hemorrhages occurring in the brain-stem accompanying cerebral swelling and tentorial herniation were excluded. The causes of death were varied, the most common being uremia, congestive failure, hemorrhage into the brain, and gastrointestinal hemorrhage. Minute hemorrhages occurred in the absence of significant nonprotein nitrogen retention, contrary to the observations of others.[3, 6, 17]

Hypertensive Encephalopathy

Hypertensive encephalopathy has been defined as an acute transitory disturbance of cerebral function occurring with severe hypertension and characterized by drowsiness, headache, vomiting and various focal manifestations, including amaurosis, hemiplegia and sometimes convulsions. Since Oppenheimer and Fishberg's [18] description of hypertensive encephalopathy there have been several reports in the literature,[3, 19, 20] but the actual nature of the condition is not fully understood and the clinical limitations and pathogenesis are a matter of controversy. Oppenheimer and Fishberg believed transient unequal arterial and arteriolar spasm to be the basis of these brief clinical episodes. Pickering, however, has stated that this mechanism is empirically unsound, and that minute vascular occlusions are a more likely cause. Nevertheless, the chief distinctions are to be made from strokes and other conditions such as uremia or cerebral anoxia due to heart failure, which are known to produce an encephalopathy and which are usually present in advanced severe hypertension. With the rigid exclusion of cases that have evidence of these other conditions, there was only one case in this series where this diagnosis could be made with reasonable assurance.

Case Report

A 36 year old male was treated for tuberculosis in a sanatorium in London, Ontario, between November 6, 1940, and April 5, 1946, where he had a right lobectomy and thoracoplasty. He was discharged "arrested," and had no recurrence subsequently. In February, 1946, while in the sanatorium, he began to complain of headaches, described as severe and throbbing, located chiefly bifrontally, over the vertex and behind the eyes, rarely spreading to the occipital region. They almost always commenced in the morning, often awakening him from sleep as early as 3 to 6 a.m., and lasting hours or even as long as three days. They were frequently associated with nausea and vomiting.

The patient was first seen in the Toronto General Hospital Out-patient Department in November, 1946, with the chief complaint of headache. Hypertension was identified at this time, being 210/135 mm. of Hg. He was treated with an extremely

low salt diet, which he followed meticulously, but without effect upon his blood pressure.

Two years before death (February, 1948), the patient was admitted to the Toronto General Hospital for severe epistaxis, which required packing to control, on four different occasions. At this time his exercise tolerance was limited to seven blocks or one flight of stairs. Examination revealed atheromatous thickening of the retinal arteries and early papilledema. The cardiac apex was 10 cm. to the left of the midline, and the blood pressure was 210/140 mm. of Hg. A two-hour renal concentration test revealed a specific gravity of 1.024 and normal day and night volumes.

In May, 1949, seven months before death, the patient was admitted to hospital because of the abrupt onset of paresthesia of the right face and arm with aphasia, lasting only a few hours. This was followed by a very severe headache, but after a sleep of 12 hours, induced by sedation, he was free of both headache and aphasia. On examination the blood pressure was 210/160 to 280/160 mm. of Hg. There were no signs of cardiac failure and no abnormalities except bilateral papilledema on neurologic examination. However, it was now observed that the two-hour renal concentration test was abnormal, with a maximal specific gravity of 1.016 and an increase in night volume. The nonprotein nitrogen was 33 mg.% and the hemoglobin was 75%. A lumbar puncture revealed a pressure of 300 mm., a negative Pandy, and 2 cells per cubic millimeter. The Wassermann was negative. An electroencephalogram was reported as showing a high percentage of medium voltage symmetric 8/second normal alpha rhythm, with 4 to 7 cycle per second slow waves from the left frontal region. The patient was re-admitted to the Toronto General Hospital on November 11, 1949, with epistaxis, which was arrested, and although he appeared to have lost a great deal of blood his blood pressure was found to be 260/100 mm. of Hg. The following day his blood pressure climbed to 300/200 mm. of Hg and he became deeply comatose, with bilateral extensor plantar responses, but overnight he completely recovered. Laboratory examination showed a nonprotein nitrogen of 63 mg.%, a hemoglobin of 91%, normal blood smear with normal platelets, and a normal prothrombin time. Urine showed on a random specimen a specific gravity of 1.016, albumin 3 plus, and a microscopic picture of 5 to 10 red cells and 5 to 10 white cells per high power field. He was discharged but re-admitted two weeks later because of congestive heart failure. On examination he appeared to be chronically ill and disoriented, with acute dyspnea. There were 3 diopters of papilledema and some exudates in the fundi. The visual acuity was markedly reduced; otherwise, neurologic examination revealed no significant findings. Coarse and medium râles were present in the lung bases bilaterally. There was jugular engorgement 7 cm. above the sternal angle, and the heart was enlarged 10 cm. to the left of the midline in the fifth thoracic interspace, with a harsh systolic apical murmur present. The blood pressure was 265/200 mm. of Hg on admission, with an average blood pressure of several subsequent readings of 230/155 mm. of Hg. The liver was palpable three fingerbreadths below the right costal margin, and the spleen could also be felt. The patient deteriorated steadily during the next few days and complained of constant headache. The nonprotein nitrogen was 117 mg.%; hemoglobin, 80%; red blood count, 4,800,000; white blood count, 9,100, with a sedimentation rate of 12. The urine showed a specific gravity of 1.015 and 4 plus albumin with gross evidence of blood. The temperature remained essentially normal until the day of death, December 8, 1949, when it rose to 101.5° F.

Autopsy Report: The heart weighed 588 gm., and the left ventricle was hypertrophied and dilated. The kidneys were coarsely granular and showed signs of long-standing hypertension, but microscopically changes of malignant hypertension predominated. The cortex and medulla of the kidneys were poorly demarcated, and the cortex was thin, with some hemorrhage evident on the right. The left kidney

was paler and smaller than the right. The glomeruli were in various stages of degeneration, and scattered over the sections were completely hyalinized glomeruli. Some of the renal arterioles had undergone fibrinoid necrosis, and almost all of the arterioles were thickened, due to subintimal hyperplasia in the majority of cases. There was a diffuse hyperplastic arteriolar sclerosis of the vessels of the spleen and of the adrenal, subpleural and peribronchial vessels. There were amyloid deposits in both adrenals.

The cerebral convolutions were swollen and somewhat flattened by edema, the right hemispheres being slightly larger than the left. (The brain weighed 1,440 gm.) Cerebral arteriosclerosis was severe. There were no other gross changes. Minute ischemic lesions, some of which were of considerable age, were found in the superficial cortex of the left precentral gyrus and left half of the pons. Sections of other parts of the brain failed to show ischemic changes, although histologic examination was limited. Arteriolar sclerosis was severe. A portion of the left corticospinal tract in the pons contained a small area of demyelinization.

The recurrent, transitory cerebral episodes and the cerebral findings at autopsy are in keeping with hypertensive encephalopathy in a case of malignant hypertension.

As noted by others,[8] the occurrence of hypertensive encephalopathy in an unmistakable form is actually rare, although it is suspected and probably correctly diagnosed more often than a figure of 1% indicates. Thus in this series there were a few that were considered as such, but because of significant cardiac and renal failure, or the possibility of cerebrovascular insufficiency with severe atherosclerosis, the picture became obscure and they were placed in the category of being merely possible cases. It would appear that these individuals die from almost simultaneous failure of more than one organ system, the deterioration occurring rapidly due to generalized vascular disease accompanying an increasingly severe degree of hypertension. In several instances the cerebral symptoms, especially rapidly fluctuating mental deterioration, suggested that the cerebral circulation was severely impaired. Numerous softenings of varying age and size (usually miliary), with necrotic, thick-walled arterioles found in many of the minute softenings, were observed throughout the brain in some of the cases with rapid mental decline.

Mental Deterioration

Of considerable importance in any disease with diffuse involvement of the nervous system is its effect on the mental processes. Hughes et al.[21] report that some degree of intellectual deterioration was evident in every one of their 51 cases. Goodman [22] observed mental deterioration and psychoses in all of six cases with severe hypertension that he reported. It is difficult to correlate psychoses with cerebral damage, but with dementia the autopsy findings can often be correlated and even predicted. Eighteen per cent of this series showed definite evidence of dementia, which ranged from failing memory and mental slowing to gross deterioration requiring institutional care.

The average age was approximately 60 years (males, 60; females, 61),

or slightly above the average for the entire series (mean age, series, 56 years). There was an almost equal distribution of males (eight cases) and females (10 cases). The period of dementia in all but two cases (ages 45 and 83 years) was between 50 to 70 years of age, i.e., in the presenile period. To ensure that the mental changes were the direct consequence of hypertension, and thereby to exclude cases with mental changes due to terminal uremia and congestive failure, criterion was adopted that the period of dementia be not less than three months before death. The longest period of dementia was six years (average period, one and a half years). Almost two thirds of the cases (11 cases) had had a previous stroke or onset with a stroke, and almost all of these (10 cases) had had, at the time of death, more than one stroke apart from a terminal hemorrhage. Although deterioration occurred with the strokes, it sometimes worsened apart from them, the patient being observed to have deteriorated without a further clinical incident. The remainder of the 18 cases (approximately a third) had onset before a stroke or had no history of strokes.

Psychometric examinations were not done, but the clinical descriptions most often referred to memory loss, with failure to recall recent events, and mental slowing (comprehension). Occasionally there was confusion, particularly terminally, with disorientation in time or space. Mood ranged from disinterest and moroseness to levity and cheerfulness. Behavior was not unusual in many, but a few showed the extremes of seclusiveness or aggressiveness. None had hallucinations, nor were actual delusions, persecutory or otherwise, described.

In most of the cases of dementia, pathologic examination of the nervous system revealed multiple small softenings, old and recent, throughout the brain. These were often small and cystic, and in some cases of severe hypertension there were also petechial hemorrhages. Hughes et al.[21] observed similar small softenings, which they found to be limited largely to the caudate nucleus, putamen and thalamus. Arteriosclerosis and arteriolar sclerosis were present in all instances, and two cases (and possibly a third) had basilar insufficiency with damage to the nervous system largely in that distribution. None showed the presenile dementia of Alzheimer or Pick, but the eldest, an 83 year old male, revealed some senile plaques in addition to numerous small softenings.

Headache

Inquiry concerning headache was made in 86 cases. Sixty per cent (52 cases) had this symptom as a significant aspect of their illness, not infrequently as the initial or chief complaint. The clinical characteristics of headache occurring in hypertension have been discussed by several authors,[23, 24, 25] and our own experience did not differ significantly. Cases were included only if the symptom was constant or recurred fairly frequently and was of at least moderate severity; this excluded those with mild and

merely occasional headache. According to Wolff,[24] the mechanism of head pain in hypertension is the same as that in migraine, arising from distention and dilatation of certain branches of the external carotid artery. However, in the few instances in this series where migraine attacks had antedated the recognition of hypertension, the headache was considered only if a change in its character established a specific relationship to hypertension.

A major difficulty in a study of headache is to establish—out of a myriad of possible causes and, in particular psychologic disturbances—its causal relationship to a specific disease state. This is especially true of headache occurring in association with hypertension. The widespread apprehension concerning the dangers of "high pressure" is very apt to induce tension headache in those who have knowledge of an elevated blood pressure. However, a number of the patients in this series (11 cases) had no knowledge of hypertension while complaining of headache. There was also the fact that the headache was frequently of a type associated with organic intracranial disease.

The average duration of headache in this series was four years; in several instances it had existed for as long as 10 years. It was most often frontal (23 cases), or occipital (16 cases), and occasionally was lateralized to one side, sometimes beginning frontally and radiating occipitally. In a number (11 cases) it was present upon awaking in the morning and tended to subside, although in others it occurred at any time and bore no relation to posture. In quality it was frequently described as throbbing and severe, with a tendency to increase in severity and frequency, sometimes becoming almost constant in the last few months. The individual average blood pressures were equally distributed to either side of the mean pressure of the entire series, indicating no consistent relationship to blood pressure level.

These features of headache occurring with hypertension are well known and the variation is therefore well recognized. With successful treatment of hypertension the headache will often subside, as in one instance in this series in which it was relieved following nephrectomy for pyelonephritis; however, because of disease in the remaining kidney, the hypertension recurred and with it the headache.

Hypertensive Retinopathy

Funduscopic examination was recorded in approximately 79% of the entire series, and the incidence of changes in the vessels, and of exudates, hemorrhages and papilledema was determined. Most of the series (87% with a record) by the time of death had fundal changes which indicated the presence of hypertension, all having such findings as venous nicking, arteriolar spasm, right angle crossings of arterioles with veins, and silver-wire effect. Apart from this, the most frequent abnormal finding was retinal hemorrhage, (65% of those in whom the examination was reported). Papilledema was present in slightly over half of the cases (55% with a

record), ranging from only slight to a very occasional severe degree of 4 or 5 diopters. The incidence of retinal exudates was slightly less (53% of those with a record). Fishberg and Oppenheimer [26] have observed that papilledema may make an appearance before hemorrhages or exudates. In this series papilledema was only occasionally observed in the absence of these.

An analysis of the individual average blood pressures in those with papilledema revealed that 75% had blood pressures above the average for the entire series. There appears to be a close relationship between papilledema and severe hypertension, which may precede a significant degree of nonprotein nitrogen retention and cerebral hemorrhage.

There has been much controversy over the relationship of papilledema to cerebral edema and increased intracranial pressure.[3, 6, 25, 27, 28, 29, 30, 31] The opinion of many has been that increased intracranial pressure associated with cerebral edema is responsible for the papilledema seen in hypertension. When the cases of cerebral hemorrhage were excluded from the group with papilledema, 80% of the remainder (22 of 27 cases) were found to have cerebral edema. A correlation between the degree of edema of the brain and papilledema could not be made from the clinical and autopsy reports of these cases, since the estimate of each was an arbitrary one, ranging from slight to moderately severe. However, in the majority with a report of cerebral edema at autopsy there had been uremia clinically, whereas in the apparent absence of cerebral edema (five cases) there was no significant evidence of uremia.

The cerebrospinal fluid pressure is of particular interest in considering the pathogenesis of papilledema. Several authors [3, 26, 33, 34] have reported an inconstant relationship of cerebrospinal fluid pressure, papilledema and cerebral edema. Clarke and Murphy [3] have stated that an elevation of cerebrospinal fluid pressure was frequently absent in cases with papilledema. In the present series lumbar punctures were done in 15 cases where there had been no cerebral hemorrhage. In 10 of these there was papilledema with the cerebrospinal fluid pressure elevated in eight. Taken in the horizontal position, the elevated pressures ranged from 190 mm. to 400 mm. of cerebrospinal fluid. In five cases there was no papilledema, and the lumbar puncture pressure ranged from 200 mm. to 225. mm. in all but one, who had a pressure of less than 180 mm. Thus the cerebrospinal fluid pressure was not elevated in all cases of papilledema, and it was found to be elevated in the absence of the latter. However, as noted by others,[35, 36] the pressure was not infrequently higher in patients with papilledema.

Cerebrospinal Fluid

Of the 15 cases where a lumbar puncture was performed in the absence of cerebral hemorrhage, the protein content and/or cellular morphology were recorded in 10. A report of the cerebrospinal fluid protein was made in only seven cases, and was elevated in four. In two of these four there had

been a stroke, whereas in the remaining two there was an elevation of protein in the absence of a history of a cerebrovascular accident. The level of protein was less than 100 mg. in all but one (who had had a stroke). All but one had multiple small softenings at autopsy, some of which were found in the cortex. In no instance were polymorphonuclear leukocytes found, though a lymphocyte count between five and 10 cells was present in a few.

Epilepsy

Convulsions of a truly epileptic nature, excluding decerebrate spasms and uremic twitchings, occur fairly frequently in advanced severe hypertension. Twenty cases (20% of the series) had epileptic convulsions, and in nine these were focal in onset. In no instance had there been a previous history of epilepsy. In 15 cases the seizures occurred terminally, particularly in the last few days of life. These were in association with cerebral hemorrhage, cerebral thrombosis, uremia and shock. Not infrequently coma persisted after the convulsion, and occasionally there was focal or generalized status epilepticus. The incidence of convulsions reported in the literature was slightly less than in this series (Schottstaedt and Sokolow,[23] 17%; Clarke and Murphy,[3] 10.5%).

The onset of convulsions months or years before death usually occurred with nonfatal cerebral hemorrhage and in those with a previous history of strokes. Although age was considered a factor by Keith et al.[38] it was not found to be of significance in the incidence of convulsions in this series.

Discussion

It is by no means rare to observe hypertension with blood pressure recordings in the moderately severe range without evidence of deterioration over a period of one or more decades. It has been repeatedly emphasized by those engaged in the study of hypertension that blood pressure recordings of even a quite high level (200 to 250 systolic and a high diastolic) do not have a major prognostic value.[1] Thus, to regard the recordings included in this series as providing an indication of the course of development of hypertensive cerebrovascular disease would be fallacious. It is probable that the difference in those with cerebrovascular disease is the relative fixity of their hypertension. Although a certain amount of lability is present, the blood pressure, even at complete rest, fails to return to normotensive levels. As their disease progresses the vascular changes tend to limit even further any fall to lower levels, and a "vicious circle" is thereby induced. When a series is selected in which all but a few of the subjects died from a cause associated with hypertension, it is evident that the series is limited to those cases where the patient is the victim of a relentless form of the disease.

The neurologic features of hypertensive cerebrovascular disease have been reviewed. "Dizziness," although a fairly frequent complaint, has

not been discussed, since in most instances it was not adequately described and thus its significance was difficult to interpret. Non-neurologic features of hypertension were not discussed in detail, although their effect upon the nervous system seemed often of considerable importance. The effect of uremia is well recognized. Less well appreciated, however, may be the effect of congestive cardiac failure in the presence of severe cerebrovascular disease, which may further impair nervous function due to anoxia.

The marked tendency to hemorrhage in hypertension is revealed in the well recognized frequency of epistaxis, intracranial hemorrhage, etc. Three cases in the series died of gastrointestinal hemorrhage, and there was one instance of bilateral adrenal hemorrhage. The cause of brain hemorrhage has been considered by Globus [10] to be invariably secondary to softening, but it is difficult to feel satisfied in circumstances where the very nature of the lesion is such as to destroy all evidence of a preceding lesion. The size of the hemorrhage would appear to be related to the size of the vessel which ruptures and, in the instance of nonfatal cerebral hemorrhage, a necrotic arteriole may have been responsible. It is perhaps remarkable that hemorrhage due to hypoprothrombinemia is rare despite chronic hepatic congestion and defective bowel absorption (congestive failure, uremia) in the stage of deterioration in hypertension. This did not appear to be a factor in the causation of hemorrhage in this series.

The finding in this series of 10 instances of nonfatal cerebral hemorrhage of a size sufficient to impair consciousness was a surprise. It becomes important when anticoagulant therapy is being instituted for patients with hypertension who are assumed to have had infarction. Cerebrospinal fluid examination may aid in the recognition that hemorrhage exists, since xanthochromia was present in the cerebrospinal fluid of half the cases. Suspicion should be aroused also if very severe hypertension is present. The level of the blood pressure readings in most of these cases was found to be well above the average for the series.

Several authors have expressed their belief in the role of increased intrathecal pressure in the production of papilledema in hypertension. Others, including Fishberg and Oppenheimer,[20] and more recently Clarke and Murphy,[3] claim a poor correlation between papilledema and intracranial pressure recordings, a view which is supported by our experience. Unless the measurement of cerebrospinal fluid pressure has been done very carefully, one cannot draw any conclusions about the degree of intracranial pressure. It is difficult to be satisfied with records made years ago by an unknown examiner, and the results of cerebrospinal fluid pressure in this series are therefore submitted with some reservation. However, cerebral edema was absent at autopsy in some instances of papilledema, which suggests that, if papilledema was the result of increased intracranial pressure, it was due to a cause other than cerebral edema. The most likely explanation, as suggested by others, is that the vascular changes in the ocular fundus

produce local ischemia with edema of the retina and optic disc. Possibly papilledema of severe degree is always due, in part at least, to increased intracranial pressure, the latter augmenting early, locally produced disc swelling.

In many instances death was not ascribable to a single cause. Seventy-five per cent of the series had a variable degree of congestive failure. Although many of these were considered to have died from congestive failure, there was frequently a moderate elevation of the blood nonprotein nitrogen terminally. The interpretation of the elevated nonprotein nitrogen in instances such as this was frequently difficult, since the factors producing azotemia may be multiple in the terminal phase. Considerable involvement of the kidneys was often observed at autopsy, even in subjects without terminal elevation of the blood nonprotein nitrogen. The incidence of death due to uremia without major cardiac or cerebrovascular complications was 10%.

Summary

A series of 100 cases of hypertension with autopsy has been reviewed, mainly with regard to neurologic features.

The initial symptoms were found to provide some indication with regard to the subsequent course of hypertension. The actual cause of death was of course not predictable, except that those with a "stroke" as the initial symptom most often died of a cerebrovascular accident.

About half of the patients had strokes due to vascular insufficiency or occlusion, and about half of these had more than one such episode. It is emphasized that in hypertension considerable damage to the brain may exist without its being apparent in the history or on clinical examination.

The mortality from intracranial hemorrhage was 31%. Ten per cent of the series survived a cerebral hemorrhage (1 to 3.5 cm. in size), although in most instances death occurred later from another hemorrhage elsewhere in the brain. Blood was present in the cerebrospinal fluid in only half of these cases, and there may therefore be difficulty in distinguishing nonfatal hemorrhage from infarction. The need for caution in the use of anticoagulant therapy in severe hypertensives with cerebrovascular accidents is emphasized.

Mental deterioration occurred in 18% of the series, and was observed most often in association with strokes, but it sometimes existed in the absence of recognizable clinical episodes. This was usually found to be associated with multiple small softenings, both old and recent, throughout the brain.

Papilledema, when present, was usually accompanied by hemorrhages and exudates. No consistent correlation was found between the presence of papilledema and increased cerebrospinal fluid pressure, or between papilledema and the presence of cerebral edema at autopsy. In those cases showing cerebral edema at autopsy, uremia had frequently existed.

Convulsions occurred in 20% of the series, most often in the few days prior to death, in association with uremia, cerebral hemorrhage or thrombosis, and shock.

ACKNOWLEDGMENT

We wish to express our thanks to Professor E. A. Linell for allowing us full access to his autopsy material and records.

SUMMARIO IN INTERLINGUA

Esseva facite un revista, con respecto al characteristicas neurologic, de 100 casos de hypertension, omnes distinguite per le disponibilitate de detaliate datos necroptic. Le casos non esseva seligite specificamente ab le puncto de vista de lor interesse neurologic.

Esseva constatate que le symptomas initial provideva certe indicationes con respecto al curso subsequente del hypertension. Obviemente, le causa precise del morte non poteva esser predicite, sed le majoritate del patientes in qui le symptoma initial esseva un attacco apoplectic moriva de un accidente cerebrovascular.

Circa un medietate del patientes in iste serie habeva attaccos apoplectic resultante de insufficientia o occlusion vascular, e circa un medietate de iste medietate habeva plus que un tal episodio clinic. Micre lesiones ischemic—sin clinic evidentia focal—esseva frequentemente trovate al necropsia. Ben que deterioration mental esseva presente in un certe numero de casos, le facto es sublineate que grados considerabile de damno cerebral pote exister sin resultar in manifestationes apparente in le historia del patiente o in le datos del examine clinic. Occlusion vascular occurrente in le distribution carotidal e basilar esseva predominantemente o completemente responsabile pro le morte in 11 casos.

Hemorrhagias esseva le causa de morte in 31% del casos in iste serie. In 10 casos (10%) un hemorrhagia intracerebral esseva discoperite con dimensiones (1 a 3,5 cm) que sufficeva a disturbar le conscietate o le functiones motori e sensori sed que non effectuava un exito mortal. In le majoritate de iste casos, le morte occurreva plus tarde in consequentia de un altere hemorrhagia in un altere parte del cerebro. Le presentia de sanguine in le liquido cerebrospinal esseva constatate in un medietate del casos de hemorrhagia non-terminal. Per consequente, il pote occurrer que le distinction inter hemorrhagias non-mortal e infarcimento es difficile. Es sublineate le necessitate de proceder cautissimemente in le uso de therapia anticoagulante in patientes severmente hypertensive qui ha suffrite un accidente cerebrovascular.

Deterioration mental occurreva in 18% del casos e esseva observate le plus frequentemente in association con attaccos apoplectic. Tamen, il occurreva que le deterioration mental se aggravava in le absentia de un attacco apoplectic, e in circa un tertio del casos le declaration del deterioration mental occurreva ante un attacco apoplectic o se disveloppava in le absentia de un historia de tal attaccos. Multiple micre areas de mollification—ancian e recente—esseva usualmente trovate in omne partes del cerebro.

Papilledema esseva presente in levemente plus que un medietate del serie total. Illo esseva usualmente accompaniate de hemorrhagias e de exsudatos. Nulle correlation regular esseva trovate inter le presentia de papilledema e un augmento del pression in le fluido cerebrospinal e nulle inter le presentia de papilledema e le presentia de edema cerebral al necropsia. In le casos in que edema cerebral esseva constatate al necropsia, uremia esseva frequentemente un constatation in le historia clinic.

Convulsiones occurreva in 20% del casos, le plus frequentemente durante le ultime dies ante le morte e alora in association con uremia, hemorrhagia cerebral, o thrombosis e choc.

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HEMOLYTIC DISORDERS: SOME HIGHLIGHTS OF TWENTY YEARS OF PROGRESS *†

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DURING the last 20 years there have been remarkable advances in our understanding of hemolytic disorders and in our ability to detect, differentiate and treat these conditions. In few other areas of medicine has progress been so rapid or so clearly attributable to the application of modern biochemical and biophysical methods to the study of the cell. In reviewing some of the recent progress in this field I have chosen to comment chiefly on observations which have added especially to our understanding of the structure, cytochemistry and metabolism of the red cell. I shall cite examples illustrating the point that some of the most common and fascinating hemolytic disorders can probably be attributed in large part to abnormalities in synthesis of protein—hemoglobin protein, enzyme protein and antibody protein.

All of us who have become enamored of the red blood cell agree with Dr. Eric Ponder that it is the product of unusually fine "biological engineering." [1] It is not the inert bag of hemoglobin that we thought it was when I first studied physiology. Although the mature mammalian red cell lacks a nucleus and is incapable of reproduction, it is very much alive and has a remarkably complex structure and metabolism. Since it is the most easily sampled of all cells, it is natural that we should turn to it for some lessons in cellular physiology, despite the fact that it has certain peculiarities.

Structure of the Red Blood Cell: I know of no really satisfactory visual model of the structure of the red cell, but figure 1, which I have modified considerably from a drawing by Ponder,[2] will suffice. At least it shows that the normal mature human erythrocyte is biconcave, and that the molecules of protein and lipid in the outer layers have an orderly arrangement. The list of constituents of the red cell given in this figure is by no means complete. We shall be particularly concerned with the hemoglobin molecules and with certain of the enzymes and substrates involved in glycolysis.

It should be pointed out that, in addition to the structural proteins, there are approximately 40 enzymes thus far identified in the normal human red cell. The exact manner in which the enzymes and other molecules are distributed throughout the cell is not known. There is good evidence, how-

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ever, that the hemoglobin molecules and other molecules close to the surface have a rather orderly arrangement, whereas those in the interior of the cell have a more disordered, but not entirely disordered, arrangement.[3]

Figure 2 shows a portion of the surface layer according to Ponder's concept.[1] The lipid molecules—that is, phospholipid, cholesterol, fatty acids and neutral fat—are represented by round-headed rectangles in a position perpendicular to the surface of the cell, while the protein molecules are pictured as being wrapped around the cell "like string around a ball." The circles at the top of the diagram represent a layer of albumin which may be

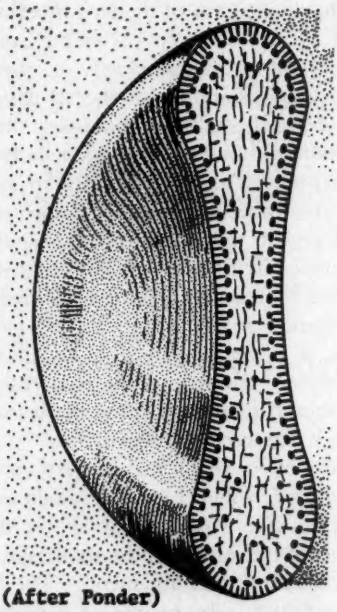

FIG. 1. Visual model of normal human red blood cell, viewed from cut surface. Molecules of lipid are represented by bars and molecules of protein by dots. The sizes of the bars and dots are diagrammatic. Molecular size is indicated more accurately in figure 2.

adherent to, or a part of, the outer surface of the cell. As we look at this diagram, we should bear in mind that many of the proteins, both structural proteins and enzyme proteins, probably have a spiral or helical molecular structure. I hope that this illustration will assist in our effort to visualize the red cell and its constituents in terms of molecules, but we must realize that this diagram is greatly oversimplified. The numerous blood group substances, for example, are among the many substances not shown here but known to be present in the outer layers of the cell.

Metabolism of the Red Blood Cell: Some of the known enzymes of the human red cell are listed in table 1. We shall be particularly interested in

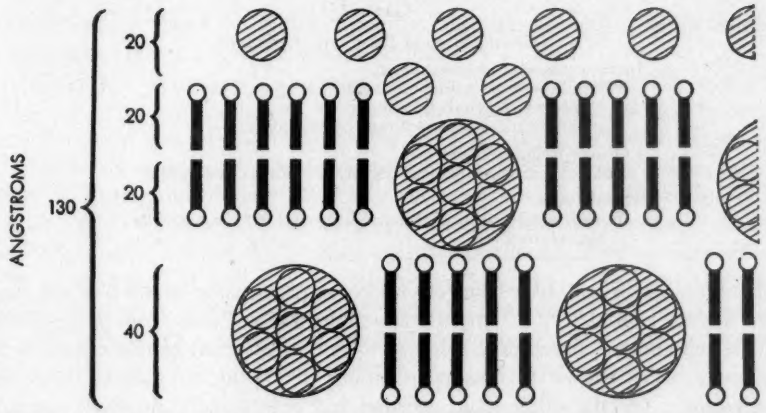

FIG. 2. Model of red cell membrane, reprinted from Ponder [1] by courtesy of *Scientific American*. Round-headed rectangles represent lipids of all types (cholesterol, phospholipid and fatty acids). Large shaded circles containing smaller circles are protein bundles cut in cross section. Circles at top represent a layer of albumin.

those involved in glycolysis. Some of these enzymes may be nonessential remnants of the nucleated life of the cell, but many of them are known to be active in the metabolism of the mature red cell.

The energy derived from glycolysis is used in a number of ways, and it is now appreciated that the very life of the cell depends on an adequate supply of energy in the form of high energy phosphate bonds.[4, 5] A large share of the energy is apparently used in ion transport and in maintaining concentration gradients. The sodium and potassium gradients between the cell and blood plasma have been most extensively studied. Reduction of methemoglobin also requires energy, and there are still other requirements that have not been thoroughly investigated. It seems possible, for example, that the shape of the cell and the maintenance of integrity of the structural proteins and lipids may depend upon energy derived from glycolysis.

HEMOLYTIC DISORDERS

During the last 15 years we have come to appreciate that much understanding can be gained by classifying hemolytic disorders, as in table 2.

TABLE 1

Enzymes Demonstrated in Human Erythrocytes

Glycolytic enzymes	Catalase
Hexose-monophosphate shunt enzymes	Urease
	Arginase
Phosphatases	Proteases
Acetylcholinesterase	ATP-ase
Glyoxalase	Methemoglobin reductase
Carbonic anhydrase	Purine nucleoside phosphorylase
Glutathione reductase	Adenosine deaminase
Pyrophosphatase	Myokinase

TABLE 2

Classification of Hemolytic Disorders

Intracorpuscular abnormalities
Hereditary (e.g., hemoglobinopathies, spherocytosis, elliptocytosis, thalassemia major)
Nonhereditary (e.g., nocturnal hemoglobinuria)

Extracorpuscular "agents"
Spleen; antibodies; chemical, physical, infectious agents

Mixed types
Both intracorpuscular abnormalities and extracorpuscular agents involved

This classification is based largely on cross-transfusion studies of the early and middle 1940's.[6, 7, 8, 9] Intrinsically abnormal red cells from patients with sickle cell anemia, hereditary spherocytosis or nocturnal hemoglobinuria, for example, were shown to disappear rapidly from the circulation of normal recipients. On the other hand, normal red cells usually survived normally after transfusion into patients with any of these diseases. Normal red cells were rapidly destroyed when transfused into patients in whom extracorpuscular agents, such as antibodies, were involved in destruction of the patient's own red cells.

Intracorpuscular Abnormalities

Hemoglobinopathies: Several of the best known intracorpuscular abnormalities are genetically determined and the patterns of inheritance are well established. Recent studies of the red cells in these conditions have done much to clarify the manner in which genes produce their amazing and sometimes disastrous effects. Work on sickle cell anemia has been especially fascinating and has already pinpointed an abnormality within the hemoglobin molecule.

Pauling et al.[10] first showed in 1949 that all of the hemoglobin molecules in sickle cell anemia are abnormal, whereas red cells from patients with sickle cell trait, the heterozygous condition, contain a mixture of normal, or hemoglobin A, molecules and the abnormal hemoglobin S molecules. Whether there are other abnormalities involved in sickling and hemolysis

TABLE 3

Arrangement of Amino Acids in Peptide No. 4 of Hemoglobin Molecules (Ingram[11,12])

Hemoglobin A	Hemoglobin S	Hemoglobin C
Histidine	Histidine	Histidine
Valine	Valine	Valine
Leucine	Leucine	Leucine
Leucine	Leucine	Leucine
Threonine	Threonine	Threonine
Proline	Proline	Proline
Glutamic acid	Valine	Lysine
Glutamic acid	Glutamic acid	Glutamic acid
Lysine	Lysine	Lysine

of sickle cells remains to be determined. Thus far, no other abnormalities of apparent significance have been described.

During the last year Dr. Vernon Ingram,[11, 12] of the University of Cambridge, reported a tedious and brilliantly executed study in which he separated by electrophoresis and chromatography the peptides yielded from the hemoglobin S molecule by systematic digestion with trypsin. The abnormality in hemoglobin S was shown to be confined to a single peptide unit, No. 4. Within this peptide a valine unit occupies the place normally occupied by glutamic acid in the seventh position of the sequence of nine amino acids, as indicated in table 3. A glutamic acid unit has a negative electrical charge, whereas a valine unit is electrically neutral; hence the difference in net electrical charge and in electrophoretic mobility of the two peptides and, in fact, of the whole hemoglobin molecule.

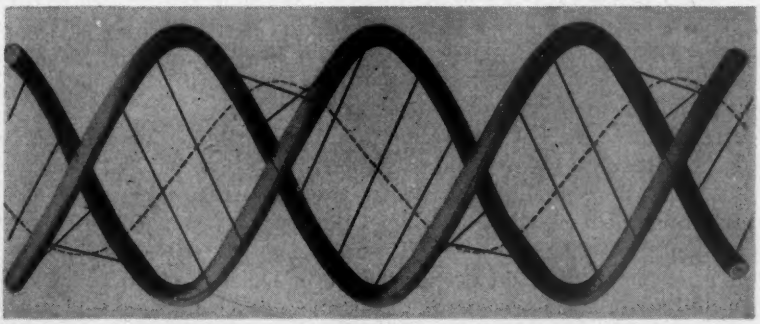

FIG. 3. Model of DNA structure, reprinted from Crick[13] by courtesy of *Scientific American*.

Ingram's colleague, Hunt, found that in hemoglobin C the abnormality was also confined to the amino acid in the seventh position in the No. 4 peptide, with replacement of a glutamic acid unit by a lysine unit instead of a valine unit, as in hemoglobin S.[12] This finding correlates with the genetic evidence that production of hemoglobin C is due to a mutation in the same part of the chromosome causing the production of hemoglobin S. Fortunately, hemoglobin C disease is much less common and less disabling than sickle cell disease, but in the homozygous form it is nevertheless a hemolytic disorder. Cells containing only hemoglobin C do not undergo sickling. The mechanism of their destruction is by no means clear, despite the precise characterization of the abnormal hemoglobin molecule.

It is indeed remarkable that in sickle cell anemia a change of one amino acid in 300 in the hemoglobin molecule is associated with the sickling phenomenon, and may therefore be importantly involved in the hemolytic and thrombotic processes with which the possessor of hemoglobin S is afflicted. It is also amazing that the responsible gene affects hemoglobin synthesis so delicately and so regularly that all but one of the 300 amino acids in the

molecule are present in the normal positions. How can a gene produce such a deviation in structure of hemoglobin or of any other protein molecule? At this point we must consider the earlier life of the red cell, when it still had a nucleus containing chromosomes.

The most recent contributions of the biochemists show that chromosomes are composed of a number of constituents, including desoxyribonucleic acid (DNA), histone, and a nonhistone lipoprotein. Functionally, the DNA is probably the most important of these, since recent studies on bacterial transforming factors and bacteriophage, as well as studies of mammalian cell nuclei, indicate strongly that DNA is the genetic material of the cell.[13, 14, 15]

DNA is a fibrous substance which, on a molecular basis, is thought to consist of two long chains or strands of nucleotides running in opposite directions and twining about each other (figure 3). The two chains are cross-linked by the hydrogen-bonded nucleotide base pairs, adenine-thymine and guanine-cytosine. The arrangement of the bases is such that, wherever adenine occurs in one of the DNA strands, thymine must occur in the opposite strand, which is hydrogen-bonded to the adenine in question. A similar relation exists between guanine and cytosine.

Crick [13] likens the DNA molecule to a long winding staircase, with the nitrogenous bases in the position of stair treads. It seems likely that each type of DNA molecule has a particular order of arrangement of its bases, and that this order somehow determines the order of arrangement of amino acids in corresponding proteins which are being synthesized under control of the gene composed of the particular kind of DNA in question.[12, 13] The properties of any given protein are in turn, to a considerable extent at least, attributable to the specific sequence of its amino acids. The control of protein synthesis by the gene or DNA in question may actually be mediated through ribonucleic acid (RNA) in the cytoplasm of cells.[13, 16, 17] RNA probably also has a helical structure. The configuration of RNA, or, more specifically, the arrangement of its nitrogenous bases, may be controlled by DNA and may in turn control the arrangement of amino acids in proteins undergoing synthesis within the cytoplasm. It should be understood, however, that the exact role of RNA in protein synthesis and the relationship between RNA and DNA are by no means established.[14, 17, 18, 19]

The recent work on sickle cell hemoglobin constitutes a landmark in the advancement of genetics. The work of Ingram [11, 12] is, in fact, the first and best example of the manner in which a mutant human gene, or altered DNA molecule, may (? through the agency of RNA) produce a minute but highly significant change in the arrangement of amino acids in a molecule of protein under construction. This demonstration would seem to be the ultimate in identification of genetically determined biochemical lesions. In sickle cell disease, as in so many other diseases recently subjected to intensive study, the biochemist has had the last word.

Drug-Induced Hemolytic Anemia: Another milestone in our understand-

ing of the red blood cell and its destruction is the fascinating series of investigations on hemolytic anemia induced by primaquine and some aniline derivatives such as sulfanilamide, naphthalene, phenacetin, acetanilid, para-aminosalicylic acid and Furadantin. Susceptible persons are mostly Negroes whose red blood cells have been shown by Carson et al.,[20] and confirmed by Gross, Hurwitz and Marks,[21] to be deficient in activity of the enzyme, glucose-6-phosphate dehydrogenase. Beutler et al. have shown that incubation of such red blood cells with acetylphenylhydrazine results in the appearance of abnormally large numbers of intracellular inclusions, called Heinz bodies,[22] and in a marked decrease in content of reduced glutathione in the cells.[23] The glutathione stability test has been utilized by Beutler et al.,[23] Childs et al.,[24] Szeinberg et al.[25] and Gross, Hurwitz and Marks [21] to detect persons susceptible to development of this form of hemolytic anemia.

The older cells in the circulation are most susceptible to hemolysis in such persons, presumably because they are most deficient in enzyme activity. Since younger cells are resistant to hemolysis by this mechanism, hemolysis tends to be self-limited. Dern et al.[26] have shown, moreover, that the red cells remaining in the circulation after hemolysis due to sulfanilamide or acetanilid are relatively insensitive to administration of primaquine.

Although there are other biochemical abnormalities in such red cells,[27] available evidence suggests that the "basic" defect is probably the deficiency in dehydrogenase which is genetically determined, quite likely by a sex-linked gene,[21, 24, 28] that is, by a gene in the X-chromosome. The deficiency in dehydrogenase and in reduced glutathione is of no consequence to the red cell unless the cell is exposed to certain substances, such as the drugs mentioned, which presumably have an adverse effect on the metabolism of the cell. Normal red cells, on the other hand, are unaffected by exposure to similar quantities of the drugs.

Favism, or acute hemolysis following ingestion of fava beans, may be associated with metabolic abnormalities similar to or possibly identical with those found in the drug-induced cases.[24, 25] Zinkham et al.[29] have demonstrated a deficiency of dehydrogenase activity in red cells from patients with favism, and Childs and associates [24] have obtained abnormal results in glutathione stability tests on red cells from persons in two Greek families afflicted with favism. The results of their studies on these families suggest, but do not prove, sex-linkage of the metabolic abnormality. Favism is most common among Greeks, Sards,[30] Sephardic Jews [31] and certain other Mediterranean stocks, including Italians, but there are no reported data on its occurrence among Negroes. It now seems possible that the apparent rarity of favism among Negroes may be due to lack of exposure of Negroes to fava beans, rather than to lack of inherited susceptibility. At any rate, we now realize that when hemolytic reactions occur after use of certain drugs or other substances, a genetically determined basis should be suspected, especially if the reactions occur most frequently in particular racial groups.

Motulsky [32] makes the point that such reactions should be regarded as "models for demonstrating the interaction of heredity and environment in the pathogenesis of disease." It is, in fact, difficult to conceive of better models. It should also be appreciated that the deficiencies in these red cells could not have been demonstrated until recently, when suitable chemical methods became available. We can expect that many inherited biochemical abnormalities of various types of cells will be demonstrated in research laboratories during the *next* two decades. It seems reasonable to predict that much of the future progress in our understanding of disease will be derived from the same general type of biochemical and genetic study recently executed so precisely at the University of Chicago,[20, 22, 23, 26, 27, 28] Johns Hopkins,[24, 29] Columbia,[21] Stanford,[21] and at the Government Hospital in Tel-Hashomer, Israel,[25, 31] by use of red cells from patients with hemolysis induced by drugs or fava beans.

Hereditary Spherocytosis: Another inherited hemolytic disorder which has been under intensive study in recent years is hereditary spherocytosis, formerly known as congenital hemolytic anemia. This condition is inherited as a mendelian dominant with widely varying penetrance or expression of the responsible gene, and is characterized by the presence of spherocytes or abnormally thick red cells in the circulation.

The immature red cells in the circulation of affected persons have normal shape; the sphering or increase in thickness/diameter ratio occurs only when the red cell has become mature. In this disorder, as in many other hemolytic states, immature red cells seem to enjoy some degree of immunity to destructive processes. Perhaps such immunity is due to differences in metabolism in the immature cell, but this possibility will require further study in each of the hemolytic disorders under consideration.

Anemia and jaundice are promptly, completely and permanently relieved by splenectomy in nearly all cases of hereditary spherocytosis, despite persistence of the abnormal shape of the red cells. These features of hereditary spherocytosis have been recognized for many years.[15, 33] What, then, is the role of the spleen in this disorder?

Whipple [34] suggested in 1941 that spherocytes might be readily trapped within the splenic pulp because the abnormal thickness of the cells would make difficult their escape through slitlike openings between the pulp and the venous sinusoids. Ham and Castle [35] in 1940 had found that spherocytes incubated in vitro at body temperature underwent lysis more rapidly than did normal red cells. They postulated that changes occurring in spherocytes while stagnating within the spleen might be similar to the changes observed during in vitro incubation, and might be largely responsible for hemolysis in spherocytic states.

Studies employing transfusion and perfusion by Dacie,[36] Emerson et al.,[37] Weisman et al.[38] and in our laboratory [39] have subsequently demonstrated that spherocytes are indeed readily trapped within the splenic pulp. Within

that site they undergo still more sphering and more rapid increase in osmotic fragility than do the normal transfused or perfused red cells which are found in the pulp in relatively small numbers during such experiments. Moreover, the normal human spleen, or the spleen in persons with nonhemolytic disorders, appears to be capable of trapping spherocytes as readily as the spleen in a person with spherocytosis.[38, 39] In this condition the abnormality is clearly within the red cell rather than the spleen, but the spleen provides environmental factors necessary for hemolysis of the defective cells.

When samples of sterile defibrinated blood are incubated at body temperature for 48 hours or longer, the degree of spontaneous autohemolysis of red cells from patients with hereditary spherocytosis is usually much greater than that of normal red cells. Selwyn and Dacie [40] showed that addition of glucose to spherocytic blood markedly inhibited such autohemolysis. We have obtained similar results in our laboratory, and have found that addition of mannose or the nucleosides adenosine, inosine or guanosine also inhibits hemolysis of incubated red cells from patients with hereditary spherocytosis.[41] It seems likely that these additives protect the spherocytes by helping to maintain energy production from glycolysis above a critical level. Jaffe and associates [42] reached similar conclusions by measuring the capacity of purine ribosides to enhance osmotic resistance of normal red cells after short periods of incubation.

During the last five years Prankerd, Altman, Tabechian and associates [43, 44] in our laboratory have studied abnormalities of carbohydrate metabolism in hereditary spherocytes by incubating the red cells with P^{32}-labeled orthophosphate and measuring the rate of incorporation of P^{32} into the various organic phosphate esters. The phosphorus-containing fractions of trichloracetic acid extracts of the red cells were separated by paper chromatography, and radioactive and chemical phosphorus was measured in each fraction. There was an abnormally small flux of P^{32} into adenosine triphosphate and 2,3-diphosphoglycerate, and an abnormally large initial flux into the inorganic phosphate fraction inside the spherocytes. Motulsky and associates [45] have obtained similar results. These abnormalities persisted after splenectomy, and were largely corrected in the majority of cases by incubating the red cells with adenosine. Lack of the corrective effect of adenosine was encountered in all affected members of four families, and may point to a variant of some significance in this disorder, which was previously thought to be a single disease.[43, 46]

The relationship of the disturbed carbohydrate metabolism to the shape of the cells and to the hemolytic process remains to be clarified. Our work to date has provided more questions than answers. It is possible that the inherited abnormality is one of structure, which in turn might account for the results obtained in the studies on metabolism and on autohemolysis. A more attractive hypothesis, however, is that the sphering and ultimate hemolysis of the red cells are related in some manner to derangement in the

energy-yielding reactions of glycolysis, which in turn may be due to deficiency in activity of one or more enzymes. Our most recent observations [44] lend support to this hypothesis, but much more study of this problem is needed.

Spherocytes may, at least provisionally, be regarded as having a metabolic handicap, which becomes clearly manifest when they are trapped in the spleen or when they are removed from the circulation and incubated in the laboratory at body temperature. In either case these red cells undergo rapid sphering and lysis. If certain sugars or nucleosides are added to the incubating cells, hemolysis is markedly inhibited, perhaps because the supposed metabolic handicap may thereby be overcome. Once the spleen is removed from these patients, the red cells have more continuous access to plasma constituents and have normal or only moderately reduced life span despite persistence of the inherited abnormalities.

It seems possible that hereditary spherocytosis may prove to be another example of abnormal or deficient protein synthesis, more specifically a deficiency in synthesis of glycolytic enzyme protein due to a mutation in the responsible gene or DNA molecule (? through the agency of RNA). This condition may prove to be analogous in certain respects to the genetically determined deficiency in glucose-6-phosphate dehydrogenase found in red cells of persons with drug-induced hemolytic anemia. In the latter condition, the drug is the environmental factor needed to cause hemolysis. In hereditary spherocytosis the splenic trap provides an environment conducive to hemolysis of the inherently defective cells.

Extracorpuscular Agents: Let us turn now to consideration of hemolytic processes due to extracorpuscular factors. In this group of disorders the red cells are presumably normal when delivered to the circulation from the bone marrow, but are destroyed in one way or another by extracorpuscular agents. Of the many known hemolytic agents only antibodies will be considered, because advances in our understanding of erythrocyte-antibody relationships have been especially rapid during the last 20 years. Interest in antibody-induced hemolysis was rekindled by the observations of Dameshek and Schwartz in 1938.[47]

Antibody-Induced Destruction of Red Cells: Studies on the capacity of iso-antibodies anti-A, anti-B, anti-Rh, anti-Kell, anti-Duffy, anti-Lewis, etc., for initiating destruction of red cells in vivo have lagged somewhat behind studies on in vitro behavior. It is already clear, however, that in the presence of specific antibodies, red cells may be destroyed by any one of several different mechanisms, or by several different mechanisms operating simultaneously. Certain antibodies are capable of rapidly lysing red cells intravascularly with the aid of complement, presumably in much the same way as red cells are lysed by such antibodies in vitro. These same antibodies, especially anti-A and anti-B from certain individuals, are the ones most capable of promoting phagocytosis of red cells by leukocytes or macro-

phages in vitro, intravascularly, in the spleen and in other portions of the reticuloendothelial system. The observations of Doan, Wright and associates,[48] Wasastjerna[49] and Swisher and Dale[50] on phagocytosis in the spleen, and by Zinkham and Diamond[51] and Bonnin and Schwartz[52] on in vitro erythrophagocytosis, are especially interesting.

Jandl, Jones and Castle[53] found that red cells sensitized or coated with the incomplete Rh antibody, anti-D, were sequestered chiefly by the spleen. Under these circumstances the spleen appears to serve as a "passive filter," and sequestration may be enhanced by the rouleaux-producing globulins of plasma. On the other hand, tagged group B red cells transfused by these investigators to a group A recipient with complete anti-B agglutinins in the circulation were sequestered chiefly in the liver. The mechanisms by which sequestered red cells are lysed within the spleen or liver are not yet known; leukocytes may be involved. Swisher, Altman and associates[54] in our laboratory have found disturbed intermediary metabolism of carbohydrate in red cells sensitized in vivo with certain antibodies, but the significance of this disturbance in relation to the lytic process remains to be determined.

Autoimmune Hemolytic Disease: Of the hemolytic states involving antibodies, one of the most fascinating and most studied is autoimmune hemolytic disease, a form of acquired hemolytic anemia associated with auto-antibodies—that is, antibodies or antibody-like substances reacting with the affected person's own red cells. Presence of auto-antibodies on the red cells or in the serum is demonstrated by use of technics such as the anti-globulin (Coombs) test,[55] developed during the last 15 years in the course of studies on iso-antibodies, especially Rh antibodies. The mechanisms by which auto-antibodies destroy red cells appear to be the same as those just enumerated for iso-antibodies.[51, 54] The relative importance of the several hemolytic mechanisms can be expected to vary considerably from case to case and from time to time in the same case, depending upon the quantity and characteristics of the auto-antibody.[9]

It should be emphasized that in most cases auto-antibodies, like most of the known iso-antibodies, are incapable of hemolyzing either autogenous or normal human red cells in vitro in the presence of complement. They may be regarded as "potential lysins," however, since certain auto-antibodies may hemolyze normal red cells treated with enzymes such as trypsin, and they may also hemolyze the abnormal red cells from persons with nocturnal hemoglobinuria.[9] Many observations of the last decade support the conclusion that the body contributes importantly, and in ways not yet understood, to the destruction of red cells initiated by antibodies.[47, 49, 53, 56, 57] In vitro systems provide only hints regarding the mechanisms that may operate in vivo. Especially mysterious is the sphering of red cells produced by certain antibodies, auto-, iso- and hetero-, over a period of about four to 24 hours after transfusion of incompatible plasma.[47, 56–60] This phenomenon has not yet been satisfactorily reproduced in vitro.

Whatever the mechanisms of hemolysis may be in auto-immune hemolytic disease, hemolysis subsides in most cases after administration of ACTH or corticosteroids, so that splenectomy can now be reserved for the more refractory cases.[61, 62] The steroids may inhibit formation of auto-antibodies, or they may somehow interfere with destruction of red cells in the presence of such antibodies. The exact mechanisms of action of steroid hormones in this disorder, as in many others, remain to be determined.

Experience in the last 15 years has revealed that about 40% of patients with auto-immune hemolytic anemia have an underlying disease, most frequently lymphoma, lymphocytic leukemia, or diffuse collagen disease.[61, 63] In fact, the presence of auto-antibodies may be the first indication of an underlying disorder. Use of the Coombs test has helped to reveal the long-term picture of auto-immune hemolytic disease and associated disorders in much the same manner as the use of the Wassermann test helped to reveal the full story of syphilis during the earlier years of this century.[64]

Striking similarities have become apparent between idiopathic thrombocytopenic purpura and idiopathic auto-immune hemolytic disease.[65, 66] Both appear to be associated with a form of auto-immunization. Both occur more commonly in females. Both are frequently relieved by administration of ACTH or corticosteroids, and in some cases by splenectomy, but relapse is a constant threat in both disorders. Both may occur simultaneously or sequentially in the same patient. Leukopenia may also occur simultaneously or sequentially with this form of hemolytic anemia,[64] but the mechanisms responsible for leukopenia seem currently to be less clear than those demonstrated in thrombocytopenic patients by Evans et al.,[65] Harrington et al.[66] and Stefanini and Dameshek.[67]

It seems to me that auto-immune hemolytic disease may be best understood if regarded as a disorder resulting chiefly from synthesis of abnormal proteins, an aberration that may be comparable in some respects to that observed in multiple myeloma [68] and in disseminated lupus.[69] Just as the characteristics of the myeloma proteins vary from patient to patient, so do the characteristics of auto-antibodies.[9] Patients with auto-immune hemolytic disease, like those with lupus, readily produce immune iso-antibodies such as anti-Rh, anti-Kell and anti-Duffy when transfused with normal red cells.[9] Moreover, they frequently produce cold-precipitable proteins or cryoproteins.[64] Certain portions of the protein-forming system of the body seem to undergo a mysterious change. Where does this occur? Available evidence indicates that certain of the most radiosensitive cells of the reticuloendothelial system produce not only antibodies but also cryoproteins and probably other abnormal proteins found in auto-immune hemolytic disease, multiple myeloma and disseminated lupus.

The microsomes, which are fragments of the endoplasmic reticulum in the cytoplasm of many types of cells, contain protein and ribonucleic acid, the RNA to which I previously referred as a likely mediator of the control

of DNA on synthesis of hemoglobin and of enzyme protein within the immature red cell. Recent work points to RNA as a template, or, to use Zamecnik's [70] term, a "printing press" controlling arrangement of amino acids in the synthesis of protein molecules. In auto-immune hemolytic disease, the tiny printing presses in the antibody-forming cells seem to respond to antigens in the patient's own red cells and in transfused normal red cells which previously evoked no response. Changes occurring in the cytoplasmic RNA of the reticuloendothelial cells may thus result in manufacture of various types of auto-antibodies, irregular iso-antibodies, and perhaps other abnormal proteins such as cryoglobulin. We do not know how such changes in RNA might come about, how they might be related, if at all, to chromosomal DNA, and what change, if any, might occur in the antigenicity of the red cells in this disease. The possible role of cytoplasmic RNA outside the microsomes may also have to be considered.[19] Nevertheless, it seems possible that changes in configuration and/or function of RNA molecules, particularly in the microsomes, of the cells in question could be responsible for the synthesis of the various abnormal proteins found in the auto-immune hemolytic disorders.

Conclusion

As we survey recent advances in our understanding of hemolytic disorders, it is apparent that much of the progress is due to appreciation of the role of disturbed protein synthesis—hemoglobin, enzymes and antibodies. It becomes clearer each month that protein synthesis is indeed a central problem in biology, and the hemolytic disorders serve admirably to illustrate this point.

Much of the progress in our understanding of hemolysis can also be attributed to the growing appreciation of the fact that the red cell is a complex, highly organized, living cell, a cell from which we can learn many lessons if we give it the attention it deserves. As each year passes we can understand more fully the meaning of the statement made by Lord Dawson [71] in 1931 that "the disease hemolytic anemia has an interest beyond itself."

Summario in Interlingua

Es presentate un revista del avantiamentos in nostre comprension de quatro typos de disordine hemolytic: (1) Hemoglobinopathias, (2) hemolyse inducite per drogas e per *Vicia fava*, (3) spherocytosis hereditari, e (4) morbo hemolytic autoimmun.

Le observationes citate supporta duo conclusiones general: (1) Alicunes del plus commun e del plus fascinante disordines hemolytic es probabilemente attribuibile in grande parte a anormalitates in le synthese de proteinas (hemoglobina, enzymas, anticorpores). (2) Un grande parte del progresso in nostre comprension de phenomenos hemolytic es le consequentia del recognition que le erythrocyto es un cellula complexe, altemente organisate, e vive.

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THE METABOLIC EFFECTS OF HUMAN AND MONKEY GROWTH HORMONE IN MAN*†

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INTRODUCTION

THE biochemical nature and diverse physiologic effects of pituitary growth hormone have been reviewed recently by a number of investigators in an international symposium,[1] by Astwood,[2] Randle,[3] Ketterer et al.,[4] Li[5] and Hays and Steelman.[6] A recent development has been the observations which suggest a degree of specificity among growth hormones obtained from different species. Normal and hypophysectomized guinea pigs fail to respond to bovine growth hormone,[7] fish growth hormone is inactive in the rat,[8] while fish and bovine growth hormones are active in intact and hypophysectomized fish.[9-12] Knobil[13-17] demonstrated that both intact and hypophysectomized monkeys fail to respond to beef growth hormone, an observation paralleling the extensive reports on the inconclusive metabolic changes following the administration of bovine and porcine growth hormone preparations in man.[18-27] One of the few exceptions to this was the observation by Carballeira et al.[28] in our laboratory that beef growth hormone administered to normal humans resulted in a lowered plasma and urinary amino nitrogen following an intravenous amino acid load. Knobil[29, 30] subsequently observed the expected metabolic changes following purified monkey growth hormone administration to young hypophysectomized monkeys. These reports stimulated our interest in studying the effects of the administration of a human and a monkey growth hormone preparation to a pituitary dwarf. These hormonal agents were found to be highly effective in establishing markedly positive nitrogen, phosphorus, calcium, potassium and sodium balances, as noted in a preliminary report.[31] Impairment of the glucose tolerance curve was evident during human growth hormone administration, whereas no change was demonstrable with the monkey growth hormone. There was a significant increase in the urinary excretion of aldosterone during administration of both growth hormone preparations, without any alteration in urinary 17-hydroxycorticoid and

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17-ketosteroid excretion. These observations have been confirmed by Henneman,[32] Pearson [33] and Raben,[34] using the same human growth hormone preparation, and have prompted a further exploration of the metabolic effects of primate growth hormone in six human beings. We wish to present our observations of these effects on nitrogen and electrolyte balance, urinary aldosterone excretion and carbohydrate tolerance.

Clinical Material and Methods

Metabolic balance studies were carried out in six subjects, three with dwarfism, one who had been hypophysectomized because of metastatic carcinoma of the breast, one with postmenopausal osteoporosis, and a "normal" medical student. The subjects received a known protein, fat, carbohydrate, fluid, sodium, potassium, calcium and phosphorus intake, and corrections were made for dietary returns when they occurred. A wide variety of determinations were performed on daily 24-hour urine collections, 72-hour stool collections and frequent blood samples. Urinary creatinine was determined as a check on the completeness of the urine collections. The data to be presented concern the effects of growth hormone on the nitrogen, potassium, phosphorus, calcium and sodium balances; on the urinary excretion of aldosterone, 17-ketosteroids and 17-hydroxycorticosteroids, and on the oral glucose tolerance curve.

The following technics were employed: sodium and potassium, by flame photometry using an internal lithium standard; urinary and stool nitrogen, by the method of Peters and Van Slyke; [35] urinary and stool calcium, by the Larson and Greenberg [36] modification of the Kramer and Tisdall method; [37] urinary and stool phosphorus, by the method of Fiske and Subbarow; [38] urinary creatinine, by a modification of the Folin and Wu procedure; [39] urinary aldosterone, by the bio-assay of Venning et al.; [40] and, in some determinations, by the chemical method of Dyrenfurth and Venning; [41] urinary corticosteroids, by a modification of the Silber-Porter reaction [42] after hydrolysis of the urine with β-glucuronidase; urinary 17-ketosteroids, by the method of Callow et al.; [43] and blood glucose, by the method of Folin and Wu.[44]

The human growth hormone was prepared from pituitaries obtained at autopsy, and the monkey growth hormone from pituitaries made available as a consequence of the poliomyelitis vaccine program. The extraction procedure was carried out by Raben.[45] In one subject a modified porcine growth hormone prepared by Raben was used. After a suitable control period the growth hormone in a slightly acid pH was administered intramuscularly every six or 12 hours. There were no local reactions to its injection, but one patient became oliguric on the fifth day and anuric on the sixth day of the administration of monkey growth hormone in a dose (20 mg. four times a day) which is now considered to be excessive.

A brief clinical description of the patients studied follows.

Case Reports

Case 1. This patient was a 13 year old male with well documented hypopituitarism secondary to a craniopharyngioma. For the four months immediately prior to this study, daily replacement therapy consisted of thyroid extract, 60 mg.; cortisone acetate, 15 mg.; and methyltestosterone, 10 mg. The latter was stopped 16 days prior to the beginning of the study, but the administration of thyroid and cortisone was continued.

Case 2. This patient was an 18 year old male with statural and sexual retardation and a skeletal age of between 13 and 14 years. Growth had ceased following a head injury with unconsciousness at the age of 13 years. Extensive investigation revealed normal thyroid and adrenal function. Methyltestosterone, 10 mg. twice a day for one year prior to admission, had resulted in an increase of 2⅞ inches in height and an increase in arm span of 4½ inches.

Case 3. This patient was a 15 year old female with well documented hypopituitarism secondary to a craniopharyngioma. For four months prior to the study she had received 37.5 mg. of cortisone acetate orally per day and no thyroid replacement therapy.

Case 4. This patient was a 53 year old female with carcinoma of the breast and widespread skeletal metastases. A hypophysectomy was performed which led to a striking remission. It was during this period that the patient received growth hormone while on cortisone acetate, 37.5 mg./day, and pitressin tannate as her sole replacement therapy.

Case 5. This patient was a 68 year old female with advanced postmenopausal osteoporosis. Growth hormone administration was part of a much longer balance study using various new anabolic steroids. There was no other evidence of systemic or endocrine disease.

Case 6. This patient was a healthy 24 year old medical student without any clinical or laboratory evidence of systemic disease.

Results

The results may be considered under three general headings: the anabolic effects, the effects on steroid excretion, and the effects on carbohydrate metabolism.

Metabolic balance studies, measuring the dietary intake and the urinary and stool output of the basic elements of protoplasm, showed that there was a prompt retention of nitrogen during and following the period of human growth hormone administration, as is illustrated in figure 1. In this and subsequent figures, the base line or zero line represents the balance of any one element during the control period, which was begun only after the patient had been stabilized on the experimental diet. Increased or decreased excretion occurring during and after treatment with growth hormone is plotted as a change from this control period base line. Thus a black area above the base line represents positive balance or retention compared with the control period, while a black area below the line represents a net loss or negative balance compared with the control period. The first figure demonstrates that the nitrogen retention was continued to a lesser degree during the nine days after stopping growth hormone. Nitrogen retention was further enhanced by the administration of monkey growth hormone. There

was also a gain in body weight with both human and monkey growth hormone. The fall in serum nonprotein nitrogen and blood urea nitrogen which occurs within 48 hours of the first dose is further evidence of anabolic activity.

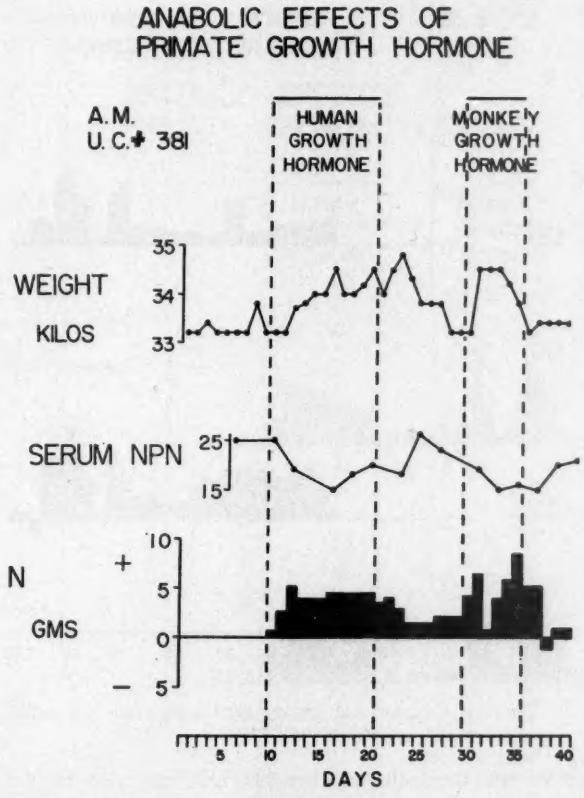

FIG. 1. Human growth hormone was administered in a dose of 10 mg. per day for three days, then increased to 20 mg. per day for a subsequent three-day period. Monkey growth hormone dosage was 40 mg. per day for three days, followed by 80 mg. per day for the next three-day period.

Figure 2 shows that there is retention of the intracellular cation, potassium, paralleling the retention of nitrogen. Evidence for an anabolic process occurring in bone can be deduced from the positive calcium and phosphorus balances which occurred under the influence of both human and monkey growth hormone, as is demonstrated in figure 3. There were no significant changes in the serum concentration of any electrolyte.

There was a marked retention of sodium (figure 4), but this was not sustained for as long a period after withdrawal of growth hormone as was

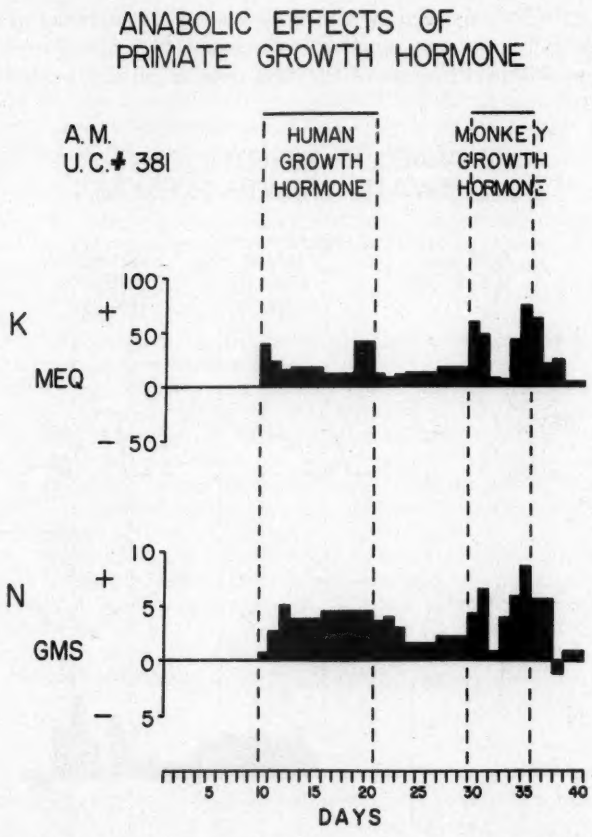

FIG. 2. The dose of human and monkey growth hormone was similar to that shown in figure 1.

the retention of the intracellular elements. It can also be seen that the period of sodium retention in this patient coincides with a marked increase in aldosterone output. This correlation may perhaps be purely coincidental, in that two patients showed an even more marked increase in aldosterone output with little or no change in sodium balance (figure 5). Neither the change in sodium balance nor the increase in aldosterone output could be related to an ACTH contaminant, since no change in either 17-hydroxycorticosteroid or 17-ketosteroid excretion occurred in any of the studies during the administration of primate growth hormone.

The results of 100 gm. oral glucose tolerance tests in these subjects are shown in figures 7, 8, 9 and 10. In these figures the solid line represents the glucose tolerance curve during the period of growth hormone administration, the broken and dotted lines represent the curves before and after

treatment, respectively. Figure 7 demonstrates that the administration of human growth hormone resulted in the production of a diabetic type of curve, with a higher, later peak and a delayed fall to the fasting level. A similar change occurred with the administration of a modified porcine growth hormone (figure 8), but no alteration in glucose tolerance resulted from the administration of monkey growth hormone in the one individual to whom it was given (figure 9).

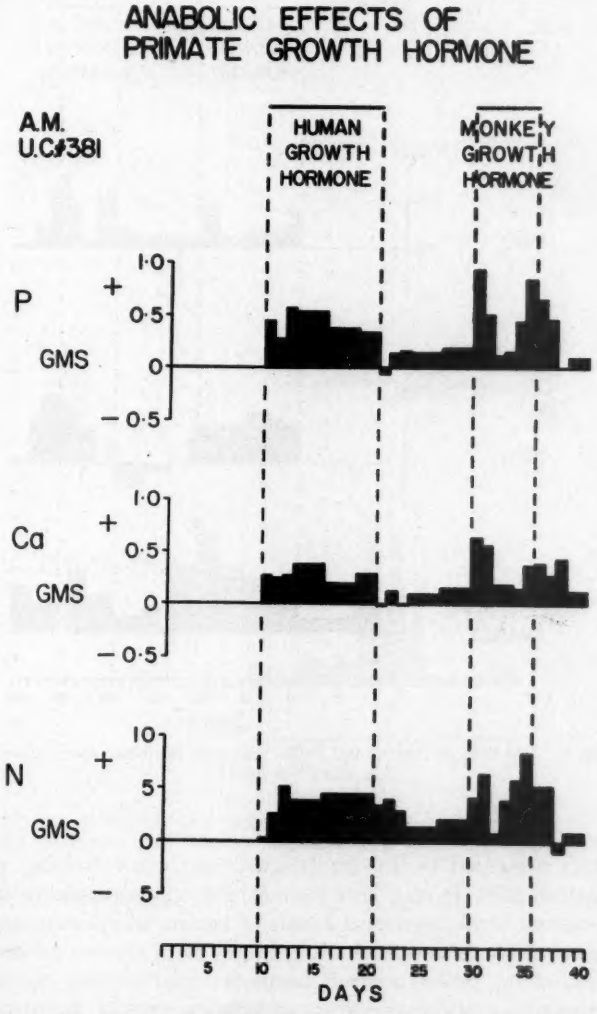

FIG. 3. The dose of human and monkey growth hormone was similar to that shown in figure 1.

In the six subjects receiving human growth hormone, a diabetic type of curve was observed in four; one normal subject showed no change. The sixth individual had a diabetic control curve and showed a normal glucose tolerance curve on the sixth day of growth hormone administration. The "diabetogenic" effect of human and modified porcine growth hormone cannot be explained by decreased peripheral utilization of glucose, since a comparable change was seen in simultaneous capillary curves (figure 10).

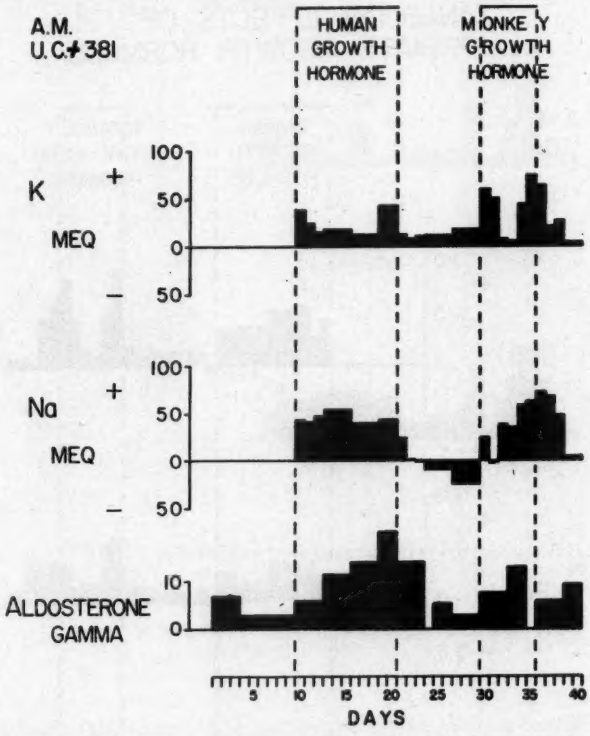

FIG. 4. The dose of human and monkey growth hormone was similar to that shown in figure 1.

DISCUSSION

The data presented in this study, particularly the striking physiologic effects obtained with human and monkey growth hormone in case 1, are in sharp contrast to the equivocal effects of bovine and porcine growth hormone in man. These observations, together with those of Knobil [29, 30] in the monkey, using simian growth hormone, lend support to the concept that the apparent ineffectiveness of nonprimate growth hormone preparations in the primate can probably best be explained in terms of species speci-

ficity. Li and Papkoff [46] have recently published data on the molecular weights, iso-electric points, amino acid composition and nitrogen-terminal groups of bovine, monkey and human growth hormone and have shown definite differences in these parameters. The existence of species specificity

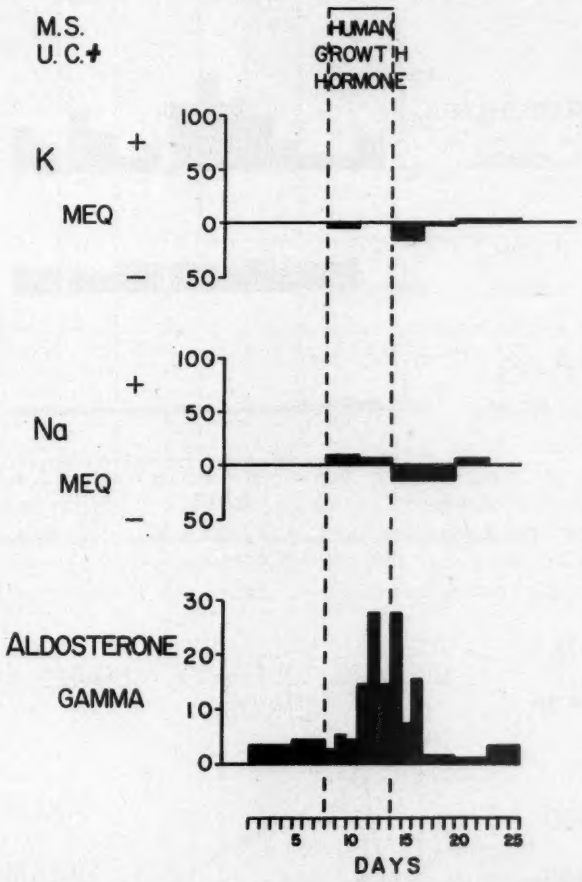

FIG. 5. Human growth hormone was administered in a dose of 5 mg. per day for three days, followed by 15 mg. per day for the succeeding three days.

might be hypothesized as being due to one of two possible changes taking place in the evolutionary scale. The data cited in the introduction suggest that the hormone from a higher species is effective in a lower one, with the converse failing to occur. This would presume that the "active portion" of the molecule has become progressively more complex as the evolutionary scale has advanced. The alternative explanation, suggested by Li,[46] is that

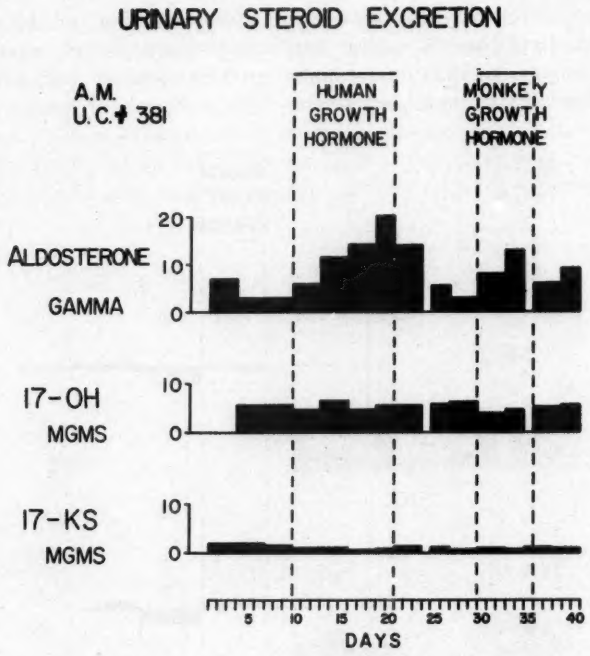

FIG. 6. The dose of human and monkey growth hormone was similar to that shown in figure 1.

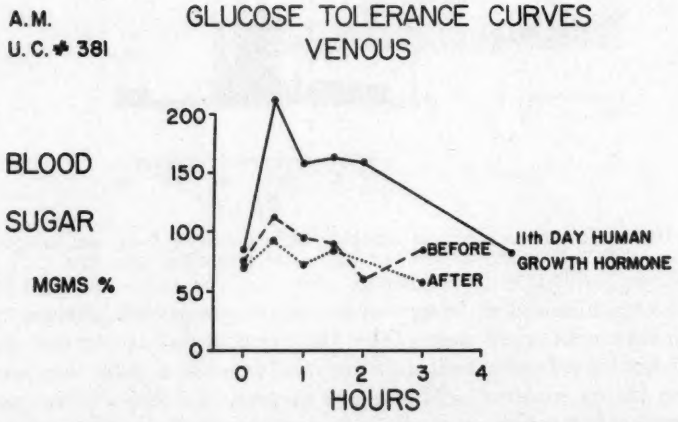

FIG. 7. Oral glucose tolerance curve during human growth hormone administration in a dose similar to that described in figure 1.

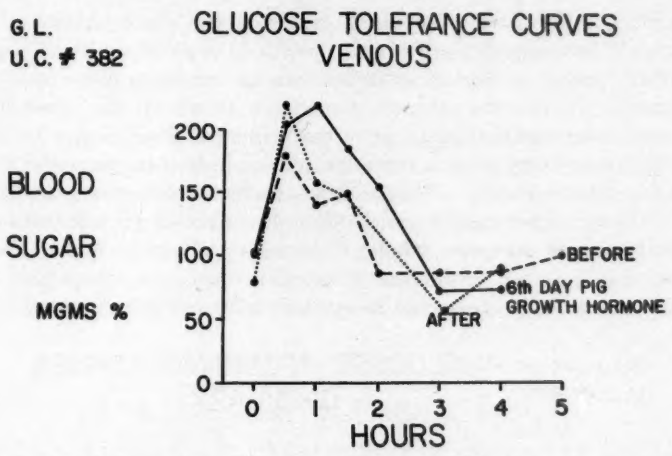

FIG. 8. Oral glucose tolerance curve during the administration of a modified porcine growth hormone. This dwarf received 10 mg. per day for three days, and 15 mg. per day for the subsequent three days.

the various growth hormones possess a similar "active core," with variations in the remaining part of the molecule accounting for the species differences observed. The latter is more attractive, since it raises the possibility of modification of readily available beef or pig growth hormones, resulting in a preparation active in man. Our data on long-term administration of growth hormone in a pituitary dwarf are still incomplete, but Raben [47] has observed a growth of 2½ inches in a pituitary dwarf receiving 2 mg. of

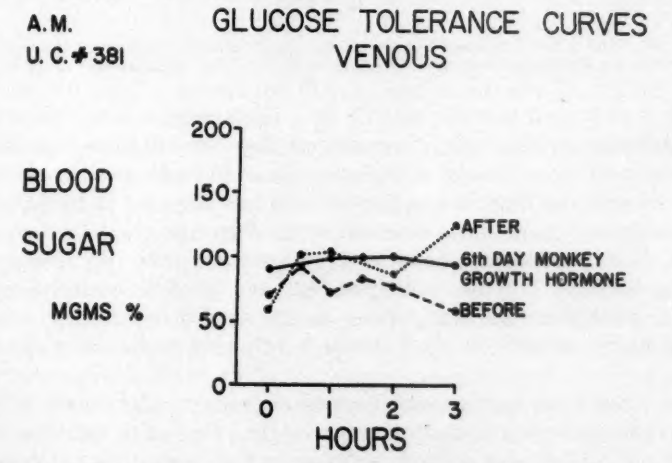

FIG. 9. Oral glucose tolerance curve during monkey growth hormone administration in a dose similar to that described in figure 1.

human growth hormone three times per week for a period of one year. Henneman [48] has recorded a 1½ inch growth in a pituitary dwarf over an eight-month period of human growth hormone administration.

In case 1, A. M., the amount of nitrogen stored on the same dose of growth hormone was dependent upon the protein intake, so that when this fell off during monkey growth hormone administration the amount of nitrogen stored was reduced. This confirms earlier observations by Gordan et al.[49, 50] in the experimental animal that the effect of growth hormone is dependent upon an adequate supply of proteins and amino acids. Another observation of interest, again best observed in case 1, is the persistence of nitrogen storage after cessation of growth hormone administration, sug-

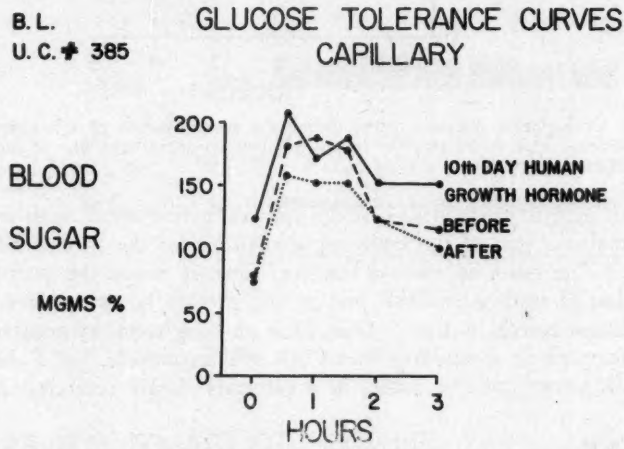

FIG. 10. Oral glucose tolerance curve during human growth hormone administration to a totally hypophysectomized female receiving 5 mg. per day for 10 days.

gesting a prolonged anabolic activity of a single dose. Although our data are inadequate at this time, they suggest that the effective dose required to produce nitrogen storage is higher in an endocrinologically normal subject. In addition, there is a suggestion that less response as to the anabolic action of growth hormone is observed in the older age group (case 5, E. S.; case 4, B. L.) whether normal or hypophysectomized. We are presently investigating the possible synergism between growth hormone and the thyroid, since there are suggestions in our data that nitrogen storage in hypopituitary patients is lower when no thyroid replacement therapy is given.

The effect of primate growth hormone in causing an increase in urinary aldosterone excretion is of great interest in relation to previous studies carried out with bovine growth hormone in our laboratories. Venning et al.[51, 52] observed a suggestive increase in urinary aldosterone excretion with

crude preparations of bovine growth hormone. However, when these experiments were repeated with highly purified preparations we were unable to demonstrate any effect on the excretion of the hormone.[53] The data presented suggest that an increase in urinary aldosterone excretion is dependent in part upon the amount of growth hormone administered. The possibility that the present preparations of human and monkey growth hormone also contain a contaminant capable of stimulating aldosterone secretion must be considered. Our data do not explain whether the sodium retention observed is mediated by the increase in aldosterone or whether it is a specific effect of growth hormone. The latter has been shown to be associated with an increase in total exchangeable sodium and the thiocyanate space.[54-56]

METABOLIC EFFECTS OF GROWTH HORMONE IN MAN

CASE	N	Ca	P	Na	K	G.T.C.	ALDOSTERONE
PANHYPOPITUITARISM (A.M.)	+	+	+	+	+	+	+
" (G.L.)	+	0	0	0	±	+	+
" (D.M.)	+	±	±	+	+	+	
NORMAL	0	0	0	0	0	0	0
Ca OF BREAST HYPOPHYSECTOMIZED	±	±	±	±	±	+	0
OSTEOPOROSIS	0	±	±	0	0	+	+

FIG. 11. This summarizes in part the experience with human growth hormone in man. (+) signifies an unequivocal response; (±) a smaller and less definite change; (0) no response. (One aldosterone determination is not available as yet and is not included in this figure.)

It is also of interest in this study that, under circumstances in which no alteration in nitrogen storage occurs, a definite increase in urinary aldosterone has been demonstrated.

It should be emphasized that the changes seen in carbohydrate tolerance are associated with short-term administration of relatively large doses of growth hormone. In the two more prolonged studies performed to date by Raben [47] and Henneman,[48] no impairment of glucose metabolism has occurred with intermittent therapy. The data presented confirm the well established observations in other species that growth hormone is diabetogenic, but it does not elucidate the mechanisms involved in this disturbance in carbohydrate metabolism. The difference in the effect of the human and monkey growth hormone on the glucose tolerance curves might be due either to differences in the length of administration of the hormone or to an actual species difference, and we feel the latter is the more likely explanation.

Growth hormone administration appears to result in three distinct types

of physiologic change, perhaps due to three separate components in the growth hormone preparations studied. These are summarized in figure 11, where it is apparent that these changes are independent of each other. There is the anabolic effect, which can be subdivided into two parts: a retention of nitrogen and potassium, the intracellular elements found in muscle and parenchymal tissues, and a retention of calcium and phosphorus, constituents necessary for increase in mass or repair of bone. There is some evidence that this may occur in the absence of significant nitrogen retention. The second major influence seen with both human and monkey growth hormone administration is the increase in urinary aldosterone excretion. The third change is the alteration in carbohydrate tolerance seen with human and modified porcine growth hormone, and occurring in all but one subject. It can be hypothesized that these latter two phenomena are due to "contaminants" in the preparations used, although there is little evidence at the present time which would suggest that the growth and diabetogenic principles of the pituitary are not identical.

Summary

The diverse physiologic effects of growth hormone in animals have been well described, but data on the effects in man have been inconclusive. Support for the concept of species differences has been provided by Knobil, who found monkey growth hormone to be physiologically active in monkeys. Our data have described some of the metabolic effects of primate growth hormone in pituitary dwarfism, a hypophysectomized patient and in normal human beings. These have included a positive nitrogen, potassium, phosphorus, calcium and sodium balance, alterations in carbohydrate tolerance, and an increase in urinary aldosterone excretion, with no alteration in urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion.

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Summario in Interlingua

Le varie effectos physiologic producite per hormon de crescentia in animales es ben documentate, sed le datos con respecto a tal effectos in humanos es pauco definitive. Supporto pro le conception de differentias inter le hormones de crescentia in varie species esseva providite per Knobil qui constatava que hormon de crescentia bovin es physiologicamente inactive in simias. Nos reporta le effectos metabolic e endocrin de hormon de crescentia ab primates in subjectos human con nanismo pituitari, in humanos normal, e in patientes human hypophysectomisate. Le effectos notate include un positive balancia de nitrogeno, kalium, phosphoro, calcium, e natrium, alterationes del tolerantia pro hydrato de carbon, e augmentos del excretion urinari de aldosterona sin alterationes del excretion urinari de 17-hydroxycorticoide e de 17-cetosteroide. Nostre experientias usque ora suggere que le administration de hormon

de crescentia resulta in tres distincte typos de alteration physiologic. Il pare que le tres es independente le un ab le alteres. Primo, il ha le effecto anabolic. Isto pote esser subdividite in duo partes: retention de nitrogeno e kalium (le elementos intracellular trovate in histos muscular e parenchymal) e retention de calcium e phosphoro (constituentes necessari pro le augmento del massa o pro le reparo de osso). Le secunde influentia major a observar in le administration de hormon de crescentia tanto human como etiam simian es le augmento del excretion urinari de aldosterona. Le tertie effecto es le alteration del tolerantia pro hydrato de carbon. Isto occurreva con hormon de crescentia human e con modificate hormon de crescentia porcin e esseva notate in omne le subjectos studiate con un exception. Il es possibile supponer que le secunde e le tertie del supra-listate phenomenos esseva le effecto de contaminantes in le preparatos usate, sed le evidentia es ancora incomplete.

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ETIOLOGIC CONSIDERATIONS OF PLUMMER-VINSON (PATERSON-KELLY) SYNDROME*

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Plummer-Vinson syndrome, as classically described, occurs mostly in women and is characterized by smooth, thin facial skin; a narrow mouth, often termed a "fish-mouth," with a tendency to fissuring at the angles; a smooth tongue; brittle nails that may be spoon-shaped, particularly on the thumb and first three fingers; a past or present history of anemia and dysphagia, often of long duration, and there is also the likelihood of complete edentia. Of these features of the syndrome, only dysphagia is an absolute requirement for diagnosis; furthermore, characteristic anatomic changes in the hypopharynx and upper esophagus must be demonstrated to be the cause of this symptom and other causes specifically excluded.

This study is based upon detailed environmental and clinical histories obtained from 150 patients with dysphagia whose difficulty in swallowing was believed to be due to the tissue abnormalities associated with the Plummer-Vinson (Paterson-Kelly) syndrome.[1-4] The data were obtained by special questionnaires and interviews with patients of the Radiumhemmet in Stockholm.

Characteristics of the syndrome are its predominance among women and its rarity in southern countries. Table 1 presents reported sex ratios of this condition.[4-11] Vinson's sex ratio suggests that he may have included males with dysphagia not due to web and stricture formations in the esophagus. On the other hand, other investigations describing only female cases may have overlooked the possibility of this syndrome in men, in whom it does occur, though infrequently.[13] The data also show that the disease has been described principally in northern countries. The recent less frequent reports of this condition may indicate its decrease.

Methodology

In 1952, together with Dr. Folke Jacobsson and the late Dr. Hugo Ahlbom, we planned a study to determine the reasons for the relatively high rate of cancer of the upper alimentary tract among Swedish women. From 1952 to 1955, 805 patients were interviewed at the Radiumhemmet by specially trained interviewers.† Patients with cancer of the upper alimentary

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† The majority of patients at the Radiumhemmet were interviewed by Mrs. Elisabeth Kallmert; others were interviewed by Mrs. Tora Nylund, Mrs. C. Lorichs and Mrs. B.

tract and larynx as well as other sites were questioned. Also interviewed was a certain number of patients with dysphagia without cancer. The present study is concerned with the etiology of Plummer-Vinson disease, and is based on 150 cases with dysphagia for which there was no explanation other than the pathologic changes associated with Plummer-Vinson disease. Detailed environmental, medical and social histories were taken on all patients. The interview information of these cases was coded and placed on IBM cards. The dysphagia cases were then matched against control cases for age, religion, education, hospital status and residence. Patients with cancer outside the upper alimentary tract who gave no history of dysphagia served as controls.

Laboratory studies included hemoglobin levels on nearly all cases and serum iron determinations on selected groups, such as dysphagia cases with-

TABLE 1

Sex Distribution of Plummer-Vinson Dysphagia as Reported in Different Studies

Author(s)	Country	Year	No. of Cases	Percentage of Females
Kelly	England	1919	(?)	100
Vinson	U.S.A.	1922	69	83
Moersch and Conner	U.S.A.	1926	65	100
Cameron	U.S.A.	1920	25	100
Witts	England	1931	13	100
Graham and Johnson	England	1931	6	100
Suzman	U.S.A.	1933	8	100
Simpson	England	1939	10	100
Waldenstrom and Kjellberg	Sweden	1939	54	96
Bingham and Logan	England	1953	16	100
Present study	Sweden	1956	150	89*
			(103)	(96)†

* Groups A, B, and C.
† Groups A and B only. See text for explanation.

out cancer, hypopharynx cancers and most esophagus cancers. The current diagnosis of the cases, a large percentage of whom had cancer, should have had no significant influence upon the present findings, since the data are based upon past rather than present or recent history.

Causes of Dysphagia: The many causes of dysphagia may be divided into organic and functional types. The former group may be further subdivided into extrinsic and intrinsic causes. The dysphagia of Plummer-Vinson disease belongs to the organic group that results from intrinsic causes.

For purposes of this investigation we have listed as dysphagic only those cases that had had dysphagia for at least two years prior to the onset

Zandren. Coding of the data was directed by Shirley McGinnis; Hjoerdis Ahlbom assisted in the tabulation of the data. Mrs. Rivkah Feldman aided in the statistical analysis of the data, which was done under the direction of Dr. Irwin Bross.

of cancer. Cases were eliminated where causes of dysphagia other than those under consideration were found. These included one case of dysphagia due to lye stricture, and 10 cases of dysphagia due to goiter which improved upon treatment of the thyroid condition.

It is possible that some of the 17 male and 133 female dysphagia cases had this symptom on bases other than the type of pathologic findings associated with Plummer-Vinson disease. For better evaluation, therefore, we have analyzed separately those cases proved to be due to the pathologic manifestation of the Plummer-Vinson syndrome and those cases for whom lesser evidence is at hand.

A. Thirty-four female cases were found in whom there was radiologic evidence of typical valvelike constriction in the hypopharynx or the esophagus. Since this type of radiologic examination is done routinely only in those cases that have dysphagia without evidence of cancer, it is quite likely that many of the other cases in the total series might have had such radiologic evidence, had this been specifically sought.

B. Sixty-nine female and four male cases were found who, in addition to dysphagia, gave a history of complete loss of teeth prior to the age of 50.

C. Thirty female and 13 male cases were found who, though they gave a history of dysphagia, had not had an x-ray study of the upper alimentary tract for possible valve defects and were not edentulous prior to the age of 50. The majority of male cases fall into this group.

The groupings are therefore based on the premise that the greater the number of specific signs and symptoms present, the more confidence can be attached to the diagnosis of Plummer-Vinson disease.

In our analysis we have matched the three groups of dysphagia cases with respective control groups for age, residence, religion and hospital status. When no difference was found among the three dysphagia groups with respect to these variables, the groups were combined and compared to the total group of controls.

Results

The statistical analyses of the data were carried out by Dr. Irwin Bross and Mrs. Rivkah Feldman and have been summarized in table 19, page 1124.

Number of Cases for Sex Distribution: The study material consists of 150 cases of dysphagia, of whom 133 are females (89%). Of the females, 34 are in group A, 69 in Group B and 30 in Group C. The respective figures for the male cases are zero, four and 13 (table 2). In the male group, therefore, a relatively greater number of cases are in group C. Thus, in Groups A and B alone the percentage of males is only 3.9.

Background Data: All of the patients in this study were clinic patients and Protestants. This condition is found primarily in the lower income groups. Only three of the entire group attended high school or college.

Residence: Since the study and control cases were matched for residence, results presented are evaluated only for the study cases (tables 3 and 4).

TABLE 2
Number of Study Cases with Dysphagia

	Group A	Group B	Group C	Total
Female	34	69	30	133
Male	0	4	13	17
				150

Residence is presented according to geographic latitude as well as crude population density. The data represent the residence of the patient prior to the age of 20. Since there was relatively little migration among the patients studied, residence data on the basis of areas where the patient lived in his adult life do not show any significant differences from those presented. The majority of cases in all groups (104 cases) had come from rural areas (table 3). Latitude 59 includes the territory of Stockholm. Patients with dysphagia who have no evidence of cancer are less likely to be sent to the Radiumhemmet Institute from outside the Stockholm area. This may account for the relatively smaller number of cases in latitude 59 within Groups B and C.

The data show a higher percentage of cases from the northern areas than would be expected from the general distribution of patients at the Radiumhemmet Institute, which serves about 4,000,000 people, of whom 20% live in Stockholm. Another 400,000 live in cities having more than 50,000 inhabitants. Thus, 70% of the people in the areas from which the Radiumhemmet draws its patient material come from rural areas or from towns with

TABLE 3
Residence of Female Dysphagia Cases Prior to Age 20 by Percentages

	Group A	Group B	Group C	Total
Stockholm	6	3	7	5
Other cities	—	3	3	2
Town	15	7	23	13
Rural	73	86	67	78
Unknown	6	1	0	2

TABLE 4
Residence of Female Dysphagia Cases by Latitude Prior to Age 20 by Percentages

	Group A	Group B	Group C	Total
55–56	3	3	3	3
57–58	12	15	20	15
59	44	27	27	31
60–61	21	16	24	19
62–63	14	28	20	23
64–65	3	10	3	7
66+	3	1	3	2

TABLE 5

Signs and Symptoms of Plummer-Vinson Disease of Female Dysphagia and Control Groups in Percentages

	Group A	Group B	Group C	Total	Controls
Dysphagia	100	100	100	100	0
Edentia	91	100	47	86	55
Anemia	71	81	73	77	53
Oral fissures	76	59	50	62	26
Brittle nails	50	54	50	52	35
Glossitis	47	35	37	38	22
Koilonychia	38	39	33	38	13

TABLE 6

Number of Plummer-Vinson Symptoms Among Female Study and Control Groups in Percentages

(Koilonychia, Brittle Nails, Glossitis, Oral Fissures and Anemia)

No. of Symptoms	Group A	Group B	Group C	Total	Controls
0	6	6	3	5	28
1	18	19	30	21	28
2	15	19	20	18	22
3	20	23	23	23	13
4	20	25	13	21	6
5	20	9	10	12	2

less than 50,000 inhabitants. Within this area virtually all of the patients treated with radiation come to the Radiumhemmet. Sixty-seven of the dysphagia cases were born and raised in regions above the 60th parallel, and 44 of the patients, or nearly one third, in areas from the 60th to the 62nd parallel.

The Disease Complex: Signs and symptoms commonly associated with Plummer-Vinson syndrome have been listed in tables 5 and 6. All of these signs and symptoms are significantly more common among the dysphagia groups than among the matched controls. The comparison group also shows many of the same signs and symptoms as the study group, though to a lesser extent. There seems to be no difference in distribution of signs and symptoms between the three study groups. Next to dysphagia, edentia

TABLE 7

Age of Edentia of Female Dysphagia and Control Group in Percentages

	Group A	Group B	Group C	Total	Control
0–20	3	3	0	3	1
20–29	15	32	0	20	2
30–39	29	30	0	23	17
40–49	35	35	0	27	17
50–59	6	0	37	10	11
60+	3	0	10	3	6

is the most clear-cut finding. These data should be fully objective. Most patients lost their teeth because of pyorrhea or looseness. Since Groups B and C were specifically set up on the basis of edentia before the age of 50 they cannot be compared with respect to edentia. In group A, 30 of the 34 cases were edentulous when first seen at the hospital. Edentia in the study group occurred significantly earlier than in the comparison group (table 7). Forty-six per cent of the patients in the study group had lost

TABLE 8

Some Previous Medical Disorders of Female Study and Control Groups in Percentages

	Group A	Group B	Group C	Total	Control
Dry skin	38	35	30	35	12
Hoarseness	23	17	20	20	5
Peptic Ulcer	9	9	3	8	2
Sore throat	6	9	17	10	10
Allergy	3	7	7	6	9
Pneumonia	12	19	26	19	10
Tuberculosis	9	0	10	6	4
Diabetes	3	0	0	1	1
Bronchitis	6	15	7	15	11

their teeth prior to the age of 39, as compared to 20% among the control group.

Review of other medical and surgical history showed the study cases to contain a greater percentage of patients with hoarseness, dry skin and, to a lesser extent, of peptic ulcer than did the comparison cases (table 8).

Most patients with dysphagia had this difficulty for more than 30 years (table 9), and stated that they had had difficulty in swallowing as long as they could remember.

TABLE 9

Duration of Dysphagia of Female Study Group in Percentages

Duration	Group A	Group B	Group C	Total
1–4	15	7	20	13
5–9	0	6	7	5
10–19	20	17	10	16
20–29	12	12	10	11
30+	53	58	53	55

Menstrual History: Analysis of the age of first menstruation as well as menopause showed no significant differences between the study and the control groups. In the study group three cases had ceased to menstruate prior to the age of 40, as compared to seven cases in the control group. In the study group 25 of the women were still menstruating, as compared to 33 in the control group.

Data on the degree of menstrual flow showed a significantly heavier flow for patients with dysphagia than for those without (table 10). A similar

TABLE 10

Degree of Menstrual Flow of Dysphagia and Control Cases in Percentages

Degree of Flow	Group A	Group B	Group C	Total	Control
Heavy	35	32	48	36	22
Moderate	56	54	43	52	61
Slight	9	13	3	10	12
Unknown	—	1	6	2	5

though less significant trend is also noted for the length of menstrual flow (table 11).

Deliveries and Siblings: Data on the number of deliveries showed that patients with dysphagia had a pregnancy rate similar to those in the control group (table 12). Thirty-four cases of the study group had never been

TABLE 11

Length of Menstrual Flow of Dysphagia and Control Cases in Percentages

No. of Days	Group A	Group B	Group C	Total	Control
2 or less	—	3	0	2	1
3–5	59	74	60	67	73
6–8	32	19	33	25	22
9+	3	0	0	1	1
Unknown	6	4	7	5	3

pregnant, compared to 43 among the controls. In contrast, 20 of the former group had had five children or more, as compared to 10 among the controls.

The pregnancy rate of both of these groups was considerably lower than was the number of siblings. Thus, only 9% of the patients with dysphagia had no siblings, as compared to 10% among the controls, whereas 48% in the former and 47% in the latter group had more than four siblings (table

TABLE 12

Number of Delivered Pregnancies of Dysphagia and Control Groups in Percentages

	Group A	Group B	Group C	Total	Control
None	26	24	27	25	36
1–2	44	42	43	42	34
3–4	12	23	10	17	19
5–6	12	7	3	8	5
7+	6	4	17	8	6

13). Determination of the position of these siblings showed that the majority of the patients themselves were among the first-born, rather than among the younger siblings.

Diet: Data on dietary intake showed that the study and control cases consumed a similar type of diet (table 14). Significant differences among

TABLE 13

Number of Siblings of Dysphagia and Control Groups in Percentages

	Group A	Group B	Group C	Total	Control
Unknown	3	1	10	4	5
None	15	7	7	9	10
1–2	26	9	27	17	10
3–4	12	26	23	22	28
5+	44	57	33	48	47

study and control groups were found only for the consumption of meat, poultry and eggs, and citrus fruits, which were less often consumed by the dysphagia cases. There were no differences in the consumption of special therapeutic diets, such as those for peptic ulcer or diabetes.

Some comments are in order upon certain items in the various food groups as they are or have been consumed by the groups under study:

Meat: The majority of the patients consumed home-preserved meat, mostly consisting of beef and veal, although farmers and laborers eat more pork, since it is cheaper. Some 30 or 40 years ago the poorer population ate even less of these meats than they eat today. The portions of meat consumed are considerably smaller than the American population consumes.

Fish: While patients living near the area of the sea or lakes may consume fresh water fish, mostly salmon, white fish and perch, two or three times a week in the summer months, these fish were rarely eaten by patients in the study group. Herring, both fresh and salted, was the fish most commonly consumed, particularly among the older patients.

Vegetables: The only vegetables occasionally consumed were carrots and pickled beet roots. While cabbage is a cheap and common food in Sweden, its consumption among the study group was surprisingly low. Pea soup made from dried peas was consumed by one-half of the cases about once a week. Turnips have been a common addition to the Swedish diet since

TABLE 14

Usual Dietary Pattern of Patients with Nutritional Dysphagia and Controls

Food	Frequency
Vegetables (green)	Rarely
Vegetables (yellow)	Rarely
Fruit (citrus)	Rarely
Fruit (other)	Rarely
Liver	Rarely
Meat	1–2/day*
Fish (fresh water)	Rarely
Fish (other)	1/day
Milk	½–1 L./day
Cheese	1–2 portions/day
Butter	3–5 pats/day
Cereal	1/day*
Potatoes	1–2/day
Bread	3–5 slices/day

* See text for details.

1914, but their consumption was also quite low among the present groups. The vegetables that were consumed were usually in the form of soups.

Fruit: The only fruit eaten with any frequency by patients interviewed in this study was the lingonberry. This fruit is very cheap and can be easily preserved even without the addition of sugar. It contains 0.3 mg. of iron and 13 mg. of ascorbic acid per 100 gm., thus being low in both categories. Another fruit, the cloudberry, is said to be commonly eaten in Northern Sweden and to be richer in ascorbic acid than is the lingonberry. Citrus fruit was virtually absent from the diet of the study group, though this fruit has been less scarce in Sweden since 1945. All other fresh fruits, such as apples, pears and cherries, are also very uncommon.

Carbohydrates: A great number of the patients ate either porridge or gruel, which is made from flour and water. In the poor families it consists mostly of water and relatively little flour. Up to the turn of the century the flour was made from barley, north of the 61st parallel. In recent years porridge and gruel are being made mostly from oats. Those families that eat gruel twice a day prepare it from semolina. South of the 61st parallel rye gruel is consumed more frequently than in the northern areas. The consumption of rice porridge was very low in our patient group. Pancakes are consumed several times a week by most families. Those who can afford it add one-half to one egg per portion. In the majority of our cases, however, only one egg was added for four persons. Margarine and lard are the materials most frequently used for frying.

Most of the patients consumed hard, crisp rye bread. Up to 50 years ago bread made of barley was the bread most commonly used north of the 61st parallel. In the past 30 to 40 years the consumption of white bread has increased, particularly in the large cities. Blood pudding and tripe are not uncommon foods in Sweden, but patients in the study group did not consume them to any significant degree.

Miscellaneous: Results for such miscellaneous items as medical therapy, blood loss, gastrectomy, infectious disease, family history, body build and oral hygiene showed no significant differences between study and control groups. The number of months nursed was slightly greater among the study cases, but this difference disappears if one adjusts for the fact that the study cases contained a greater number of pregnancies.

Laboratory Data: The only laboratory data taken routinely were serum iron and hemoglobin determinations (tables 15 and 16). Serum iron determinations were obtained relatively routinely only for the dysphagia groups. The laboratory data given are those obtained upon the first hospital admissions and thus before any medication or blood transfusions were given to the patient. This, of course, does not exclude the possibility that some of the patients may have received such medication prior to entering the hospital. Half of the study group had normal hemoglobin levels (12 and 14 gm. %), and there were only 11 cases that had a hemoglobin of less than

10 gm. %. Similarly, the data indicate a relatively large number of cases to have normal serum iron levels. Seventy-three cases had serum iron levels above 69 gamma, which is considered to be the lower limit of normal for women, and 23 had levels below 50 gamma. These data demonstrate that a significant number of female patients, even with well established Plummer-Vinson disease, have normal hemoglobin and serum iron levels.

TABLE 15
Serum Iron Level of Female Dysphagia Cases in Percentages

Serum Iron in Gamma Per Cent	Group A	Group B	Group C	Total
Under 29	7	13	6	10
30–49	13	10	12	11
50–69	10	11	19	12
70–89	10	21	6	16
90–119	27	24	25	25
120+	33	22	31	27
No. of cases with known values	30	63	16	109

This, of course, does not deny that these patients may have had anemias and sideropenias early in their lives.

Additional Comparison Group: From the general control group of this study 106 female cases without anemia were chosen as controls to the 133 cases with dysphagia. These controls were not matched but their ages and residence distribution were similar to those of the study cases. The purpose of this separate analysis was to determine whether some of the differences established between the study group and the matched analysis may be less pronounced in view of the fact that the patients in the matched controls may have had some of the clinical features of Plummer-Vinson disease themselves. It was for this reason that a group of nonanemic women were chosen, very few of whom had clinical signs and symptoms of Plummer-Vinson disease. All of the signs and symptoms associated with Plummer-Vinson disease were significantly more common among the dysphagia cases at the 1% level. It is of interest that the degree of menstrual flow,

TABLE 16
Hemoglobin Level of Female Dysphagia Cases in Percentages

Hemoglobin in gm. Per Cent	Group A	Group B	Group C	Total
Less than 9.9	9	9	10	9
10–11.9	44	43	41	39
12+	47	49	49	52
No. of cases with known values	32	60	29	121

TABLE 17

Diagnosis of Female Dysphagia Cases by Cancer Site in Percentages

Site	Group A	Group B	Group C	Total
Hypopharynx	26	52	37	42
Lip	3	0	0	1
Bucca/Gum	3	12	3	8
Tongue	6	9	10	8
Palate	0	0	3	1
Esophagus	0	13	3	8
Malignant, others	9	6	24	10
Benign disorders or simple Plummer-Vinson syndrome*	53	8	20	22

* The majority of cases admitted for Plummer-Vinson disease.

which in the previous analysis was significant at the 5% level, is now significant at the 1% level, and that length of flow was found to be less among the comparison group, a difference significant at the 5% level. The dietary deficiencies in relationship to meat, poultry and eggs as well as to citrus

TABLE 18

Some Characteristics of Male Dysphagia Patients

Age Distribution

30–39	40–49	50–59	60+
2	3	6	6

Residence by Latitude

55–56	57–58	59	60–61	62
4	2	5	2	4

Diagnosis

Hypopharynx Cancer	Esophagus Cancer	Tongue Cancer	Vocal Cord Cancer
6	2	2	2

Buccal Mucosa Cancer: 2

Miscellany: 3

Dysphagia—17

Duration in Years

1–4	1
5–9	1
10–20	2
21+	13

Edentia—8

Age of Edentia

20–29	2
30–39	3
40–49	1
50+	2

Oral Fissures—7	Sideropenia—4 (out of 9 who had serum iron analysis)	Anemia —1 (out of 15 who had hemoglobin analysis)
Anemia —6		
Glossitis —5	Koilonychia—1	Gastrectomy—0
Brittle Nails —4	History of blood loss —1	

fruit, which were found to be significantly less at the 5% level in the analysis of the matched controls, were not found to be significantly different in this comparison group.

Relation to Specific Cancer Types: Due to the nature of admissions to the Radiumhemmet, the patients included in this study have either Plummer-Vinson dysphagia or cancer (table 17). The majority of patients with cancer had involvement of the upper alimentary tract. Of 114 female patients with cancer and Plummer-Vinson syndrome, 93, or 81%, had this cancer in the area of the upper alimentary tract. The most common site of this association is the hypopharynx—42% of the cases.

Male Cases: In table 18 we list some of the pertinent findings of male cases with dysphagia. Among these cases only five had, in addition to dysphagia, a variety of other signs and symptoms associated with this disease complex and had lost their teeth prior to the age of 40.

Among the patients who had analysis for serum iron levels, four had sideropenia at levels below 70 gamma. There was a history of a moderate amount of blood loss in one case. The dietary pattern of these patients is quite parallel to that previously described for the female cases. Four of these cases came from areas higher than the 63rd latitude. Three of the cases had cancer of the lower hypopharynx.

The alcohol consumption for most of the male patients is rather high, and it may well be that some of these dysphagia cases may not be on the basis of valvular defects but rather on the basis of chronic pharyngitis. Because of the relative infrequency of this condition in male patients, one case history is presented in brief form:

Case Report

This patient was a 37 year old farmer born in northern Sweden at approximately Latitude 60° North, Longitude 20° East. As long as he could remember he had had dysphagia: "The food always seems to stop in my throat." At the age of 14 he was said to have been anemic, and took an iron preparation and vitamins for a period. He had suffered intermittently from a painful tongue and cracking of the angles of his mouth. His nails were always brittle and broke off so easily that they never had to be cut. At about the age of 20 he had lost all his teeth because of "looseness" and caries. At 28 he had had an episode of "nephritis" with epistaxis, albuminuria and hematuria. At 31 he developed polyarthritis.

Family History: The patient's father is living and well at the age of 85. His mother had died at 54 of peptic ulcer. The patient was the second youngest of 10 children, six girls and four boys. The second oldest girl had had dysphagia and anemia, and had died at the age of 30, of presumed heart disease. The youngest girl currently has anemia.

Dietary History: The patient usually ate breakfast and supper at home, taking lunch with him to work. After the age 28, when he had "nephritis," he was supposedly on a "salt-free" diet. He stated that he ate food hotter than the other members of his family.

The dietary pattern was as follows: Salted meat of various types was eaten in small portions twice a week, but he never had liver or poultry. Small salt herrings

were eaten twice a month, but no fresh water fish. He virtually never ate fresh green vegetables or fresh fruit of any kind. Carrots and turnips were taken twice a month only. He drank a half liter of milk daily, and ate one or two portions of cheese, two to five pats of butter, one or two potatoes and three or four slices of bread. Cereals were eaten twice daily as barley or rice and pancakes made of flour and eggs once a day. Sugar was consumed in large quantities, 50 to 100 pieces a day, usually with coffee. When he was out in the woods, sugar might be his only food for a whole day.

He chewed one-half hectar of tobacco a week which was consciously swallowed. Alcohol was taken primarily at weekends, when he drank approximately 1 L. of schnapps.

Physical Examination: The patient weighed 132 pounds and was 5′ 7″ tall. His skin felt moderately smooth. Rhagades were present. The mouth was edentulous, with normal mucous membrane. The tongue was smooth, but papillae were present. The nails were well rounded but brittle. The liver and spleen could not be felt, and the remainder of the physical examination was not remarkable.

Laboratory data showed a hemoglobin of 104%; red blood cells, 5.3 million; white blood cells, 4,500, with a normal differential count; platelets, 152,000; serum protein, 7.4 gm. %; serum iron 190 gamma %.

This patient was diagnosed upon biopsy to have a squamous cell carcinoma of the lower hypopharynx.

The data demonstrate that Plummer-Vinson disease may occur in men, although with a much lower incidence than in women.

Discussion

The fact that obvious signs of an iron deficiency state are so commonly found in patients with dysphagia of the Plummer-Vinson type has led Waldenstrom and Kjellberg [11] to suggest that the name "sideropenic dysphagia" be attached to this syndrome. However, final proof that a simple cause-and-effect relationship exists between the chronic iron deficiency state and the dysphagia is not yet available, and the possibility of other interrelated factors, perhaps of a nutritional nature, cannot be excluded. It is pertinent, therefore, to consider the observed manifestations of the Plummer-Vinson syndrome and to attempt to relate these to each other, to the epidemiology of the syndrome, and to what is known about the nutritional status of populations in which the syndrome occurs with greatest frequency. Figure 1 represents a schematic outline of some of the known and postulated interrelationships which may be of etiologic importance in the condition.

Incidence and Etiology of an Iron-Deficiency State: An anemic state, as manifested by a hemoglobin level of less than 12.0 gm., was demonstrated in 46.5% of the group of dysphagic patients in the present study at the time of their examination at the Radiumhemmet. Only 27% of the group had serum iron levels less than 69 gamma %. As one would anticipate, the majority of the group with low serum iron levels also demonstrated low hemoglobin values, so that there was a high degree of overlap in these two findings. A total of 77% of the dysphagic group gave a history of anemia at some time in their lives.

These figures should be compared with available figures for the incidence of various objective manifestations of iron-deficiency states in the general population of northern Sweden. Odin found "hyponormal" hemoglobin values in 43% of males and 32% of females in a series of 3,760 examinations among such a population in 1929–1931.[14] Waldenstrom examined 152 females in the province of Upsala in 1940–1941 and reported that 29% had serum iron levels of less than 55 gamma %.[15] He further pointed out that a low serum iron level, low hemoglobin level and epithelial manifestations of iron-deficiency, such as glossitis and oral fissures, might be present inde-

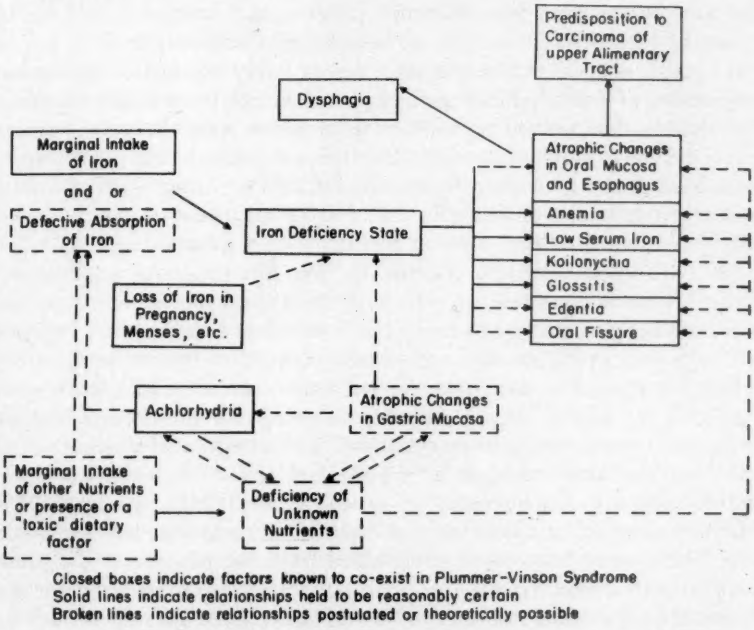
Predisposition to Carcinoma of upper Alimentary Tract
Dysphagia
Marginal Intake of Iron
and or
Defective Absorption of Iron
Iron Deficiency State
Atrophic Changes in Oral Mucosa and Esophagus
Anemia
Low Serum Iron
Koilonychia
Glossitis
Edentia
Oral Fissure
Loss of Iron in Pregnancy, Menses, etc.
Achlorhydria
Atrophic Changes in Gastric Mucosa
Marginal Intake of other Nutrients or presence of a "toxic" dietary factor
Deficiency of Unknown Nutrients
Closed boxes indicate factors known to co-exist in Plummer-Vinson Syndrome
Solid lines indicate relationships held to be reasonably certain
Broken lines indicate relationships postulated or theoretically possible

FIG. 1. Schematic diagram showing known and theoretic steps believed to be precursors of the Plummer-Vinson syndrome.

pendently in some cases, so that any single criterion could be expected to underestimate the over-all incidence of iron-deficiency state in a given population. Of the matched control group in the present study, none of whom had dysphagia, 53% gave a history of anemia at some time in their lives, an incidence significantly less than that in the dysphagic group.

It is quite clear that iron deficiency is, or has been, prevalent in the female population of northern Sweden, and in the absence of any evidence of a widespread cause for occult blood loss this must be due to an inadequate intake of iron or to defective absorption of iron, or a combination of these two factors.

On the basis of dietary surveys among several population groups, Odin calculated the mean iron intake on the least adequate diet he encountered (designated LIa) as 11.0 mg. per day for females over age 15, and 17.5 mg. per day for males, minimal values being 8.4 mg. and 10.4 mg., respectively.[14] Comparison of these figures with the currently recommended allowance of 10 mg. per day for males and 12 mg. per day for premenopausal females suggests that a marginal deficiency might exist for a substantial number of the female population.[16] However, the reliability of the food values quoted is uncertain in view of the known difficulties in analytic methods then available. Lundholm noted that the iron intake of healthy siblings appeared to be no different from that of anemic patients, and concluded that the importance of a low iron intake, per se, had not been demonstrated.[17]

It is also notable that while the present study showed a significantly lower intake of meat, poultry and eggs and citrus fruit in the dysphagic group than in the matched controls, 53% of whom were themselves anemic, dietary differences did not exist when the comparison was made with a nonmatched group of women specifically selected as being without anemia. There seems to be reason to doubt that a marginal intake of iron is the sole cause of the iron-deficiency state in this population group.

No evidence is available relating to iron absorption in patients with Plummer-Vinson syndrome or with hypochromic anemia in northern Sweden. Lundholm attempted to carry out iron-balance studies, but expressed little confidence in his results, and found the work of others inconclusive.[17]

Iron absorption in the human or the experimental animal is known to be affected by several dietary factors, including the presence of reducing groups such as ascorbic acid or cysteine,[18] low to moderate amounts of calcium [19] and pyridoxine deficiency,[20] all of which tend to increase iron absorption. Conversely, the presence of excessive dietary phosphates,[21] phytic acid,[22] or calcium,[19] or a deficiency of copper,[23] is known to decrease absorption. The dietary histories were obtained from the patients in the present survey in such a manner that the quantitative data are more valid for comparative than for absolute assessment. However, the general dietary pattern appears to be similar to that found by Odin, who characterized the least adequate diet he encountered in northern Sweden as marginal in total and animal protein, and perhaps marginal in thiamine, riboflavin and ascorbic acid and vitamin D in winter.[14] The diet is deficient in fresh vegetables and fruits, particularly citrus fruits, and also in fresh meat and fresh fish. On the other hand, it is quite excessive in carbohydrates.

The available quantitative and qualitative evaluations of the diet of the population in which sideropenic dysphagia occurs do not permit very precise assessment of nutrient intake. The intake of ascorbic acid must be comparatively low in the population studied. Moore has recently demonstrated [18] that the simultaneous administration of ascorbic acid with tagged iron would improve iron absorption from the intestinal tract, and hence paucity of this

vitamin might be a contributing factor to the development of an iron-deficiency state.

In addition, it is of interest that scurvy is the only vitamin deficiency disease known to cause loss of teeth. The frank manifestations of this disease are rarely found in patients with the Plummer-Vinson syndrome, but throughout the entire population group of northern Sweden ascorbic acid intake has been marginal in the past. The high intake of cereals containing phytin may also be an adverse factor. Calcium and phosphate intakes do not appear to be excessive, which would favor absorption, and little can be deduced about total copper intake, although there is nothing to suggest that this should be grossly abnormal. The possibility that other nutritional factors, such as trace elements, might be involved in either iron absorption or iron metabolism certainly merits investigation.

The similarity of oral mucosal changes in Plummer-Vinson syndrome to those noted in supposed B-vitamin deficiency states has been noted by several authors,[24] ariboflavinosis being especially implicated. Miller and Rhoads [24] produced somewhat similar changes in dogs by a diet deficient in B vitamins, especially riboflavin.[25-27] Treatment with this vitamin has produced improvement in oral fissures but not in dysphagia.[26] However, Hurst [28] noted that the diet may be normal, and treatment with single or multiple vitamins frequently fails to produce any improvement.[7, 29, 30] Plummer-Vinson syndrome seems to have little in common with other vitamin deficiency states, although loss of teeth is seen in scurvy, and low blood levels of ascorbic acid are reported to be common in the entire population group in which Plummer-Vinson syndrome occurs.[31]

Achlorhydria is commonly found in hypochromic anemia. Whitby and Britton put the incidence at over 80%.[32] Lundholm found an incidence of 67% in anemic patients in northern Sweden and in 32% of nonanemic controls.[17] However, it is not certain whether the anemia or the achlorhydria is primary, and the importance of the finding is controversial. Wintrobe concludes that achlorhydria alone will rarely cause iron deficiency, but that when other limiting factors are operating the achlorhydria may be a precipitating factor.[33] This leaves unanswered the problem of the causation of the achlorhydria, which might presumably be dependent upon other dietary factors, or be a constitutional defect. Lundholm found atrophic gastric mucosa in 28 of 43 patients with hypochromic anemia on gastroscopy,[17] and there was a high correlation of this finding with achlorhydria, but the significance of this observation is unknown.

The predominance of women over men in the series of patients with Plummer-Vinson syndrome suggests that the iron losses in menstruation may be a contributory factor. This is further supported by the finding of statistically significant differences in degree and length of menstrual flow between dysphagia and matched and unmatched control groups in the present study. Lundholm, however, was unable to establish this relationship.[17]

Moore calculates that the additional requirement for dietary iron for women over that for men (assuming 10% absorption) is 1.0 to 1.5 mg. per day.[16] Small as this figure is, it might reasonably represent the difference between positive and negative iron balance where other factors are marginal.

Mechanism and Etiology of Dysphagia: For many years the mechanism of dysphagia in Plummer-Vinson syndrome was much in doubt. Vinson and others had considered the difficulty in swallowing to be a result of hysteria.[8] Kelly and Paterson deserve the credit for first recognizing the dysphagia to be on the basis of organic findings as a result of web formation and strictures.[1, 2] Their findings have been confirmed by several autopsy studies of patients with this disorder, which have demonstrated that the stricture in the hypopharynx and the esophagus was brought about by an atrophy of the epithelium as well as an atrophy of underlying musculature. Similar findings were noted in the mucosa of the oral cavity, and thus explain the atrophic appearances of the surfaces of the mouth.[34] While pathologic findings present an adequate explanation for the clinical signs and symptoms at hand, they do not explain how these findings are brought about. It is pertinent to speculate on the basis of available evidence on the cause or causes for these pathologic findings.

The association of one or more manifestations of an iron-deficiency state with the dysphagia of Plummer-Vinson syndrome is so frequent that some justification exists for the assumption of a cause-and-effect relationship between them. In the present survey 77% of the dysphagic group gave a history of anemia at some time in their lives, although less than 50% had objective evidence of this at the time of examination. The geographic distribution of Plummer-Vinson syndrome appears to parallel that of observed iron-deficiency anemia in Sweden, both being much more common in the northern parts of the country. The sex distributions of Plummer-Vinson syndrome and iron-deficiency anemia are also similar.

The point has been made in the past that dysphagia, by limiting the intake of certain foods and especially meat, will contribute to iron-deficiency and hence could be the cause rather than the effect of anemia and the other manifestations of the iron-deficiency state. However, in many cases (for example, that of Hurst [28]), anemia is noted to precede the onset of dysphagia. Finally, the most convincing evidence in favor of iron-deficiency playing a direct role in the etiology of the dysphagia is the demonstrated fact that iron therapy alone can partially or completely cure the symptom in many cases unless irreversible anatomic changes have occurred.[10, 15, 35]

Certain inconsistencies exist, however, which suggest that an iron-deficiency state may not be the sole etiologic factor in the development of dysphagia. Despite the frequency of apparently chronic iron deficiency in the populations studied in the period 1929 to 1937, the over-all incidence approaching 40% in Odin's studies, dysphagia was present in less than 20% of those with anemia, according to Lundholm.[17] Furthermore, he

found an insignificant correlation between the color index of his patients and the presence or absence of dysphagia. Conversely, in the present series 23% of the dysphagics apparently denied any previous history of anemia. It is curious also that dysphagia should be so rare a concomitant finding of hypochromic anemia outside the northern latitudes, a fact usually explained by the known high incidence and chronicity of the iron-deficiency state in those areas. Consideration should perhaps be given to the possibility of other environmental factors in the etiology of the esophageal changes under discussion. Mention has already been made of possible interrelationships of nutrients affecting iron absorption or metabolism. It is also theoretically possible that nutritional factors other than dietary iron content might play a direct or an indirect role in causing the mucosal changes. The presence of endogenous, constitutional factors also seems likely, since neither anemia nor dysphagia is a constant finding within the female members of one family, despite apparently identical environments.

Relationship of Atrophic Changes to the Development of Cancer: There seems to be little doubt that the characteristic lesion of the Plummer-Vinson syndrome—atrophy of the upper esophageal musculature and mucosa—predisposes to ultimate malignant change. Wynder et al.[36] found that dysphagia had been present for at least two years prior to a diagnosis of carcinoma of the upper hypopharynx in 71% of the 24 female cases in their series. The comparable figure for cases of carcinoma of the lower hypopharynx was 69%. Other symptoms or signs of an iron-deficiency state, such as anemia, oral fissures, koilonychia, brittle nails and glossitis, were also present in a significantly higher percentage of the patients in these groups than in a matched control group. The possibility exists that these signs and symptoms were due to the carcinoma rather than being a part of a predisposing syndrome. But this is unlikely in the case of dysphagia which had been present in the majority of patients for more than 20 years before the diagnosis of a malignant lesion was made. Wynder et al.[36] also noted the similarity of geographic incidence of Plummer-Vinson syndrome and carcinoma of the hypopharynx in Sweden, both being much more common in northern latitudes. The sex incidence is also similar. They concluded that the excess of cancer of the upper alimentary tract in Swedish women over that of British, Danish and American women could be accounted for, at least in part, by the markedly increased existence of Plummer-Vinson syndrome in Sweden.

It is clearly of great importance to determine the possible relationship between the atrophic processes leading to the dysphagia of Plummer-Vinson syndrome and the subsequent development in such tissues of malignant change. The process might be entirely unrelated to any primary biochemical defect, constituting rather a nonspecific reaction to "chronic irritation," especially where stenosis is likely to lead to stasis and the possible pocketing of undigested food particles. Such an explanation may be suggested by

the observation that malignant change tends to occur above the area of web formation, rather than in the web or below it.[10, 37, 38] However, atrophic changes in both muscular and mucosal layers of the esophagus are not usually localized,[34] and it is possible that there exists a biochemical defect, representing perhaps the end result of a prolonged deficiency of an essential

TABLE 19

Factors Studied

Factors	Results	
1. Symptoms		
Oral fissures	*	
Glossitis	*	
Koilonychia	*	
Brittle nails	*	
Edentia	*	
2. Other Diseases and Therapy		
Rheumatism	†	(controls more than dysphagia)
Thyroid	n.s.	
Peptic ulcer	n.s.	
Anemia	*	
Sore throats	n.s.	
Sinusitis	n.s.	
Pneumonia	n.s.	
Tuberculosis	n.s.	
Lung abscess	‡	
Salivation	‡	
Dry skin	*	
Hoarseness	*	
Night blindness	n.s.	
Bronchitis	n.s.	
Bronchiectasis	n.s.	
Nephritis	‡	
Diabetes	‡	
Body build	n.s.	
Syphilis	*	
Sulfa therapy	‡	
Thyroid therapy	‡	
Vitamin therapy	‡	
Antibiotic	‡	
Insulin	‡	
Antihistamine	‡	
Analgesics	‡	
Hormones	‡	
Iron/Liver	†	(reversal of groups 1 and 2 and 3)
X-ray	‡	
3. Dietary Deficiencies and Special Diets		
A. Deficiencies:		
Meat, poultry and eggs	*	
Fish	n.s.	
Vegetables	n.s.	
Cheese	n.s.	
Citrus fruits	*	
Other fruits	n.s.	
Bread and cereal	n.s.	
Potatoes	n.s.	
Milk	n.s.	
Butter	n.s.	
B. Special Diets		
Salt-free	‡	
Ulcer	n.s.	
Diabetic	‡	
Gall-bladder	‡	
Reducing	‡	
Starvation	‡	
Fad	‡	
Other	n.s.	
4. Factors Related to Possible Iron Loss		
Menarche	n.s.	
Degree of flow	†	
Length of flow	n.s.	
Number of deliveries	n.s.	
Menopause	n.s.	
Number of siblings	n.s.	
Rank of patient	n.s.	
Blood loss	n.s.	
Months of nursing	n.s.	

* Significant at 1% level.
† Significant at 5% level.
n.s. Not significant.
‡ Too few cases to test.

metabolic component, which leads ultimately and in one continuous process to the metabolic disorders which constitute malignant change.

Beutler [39] has recently reported that levels of cytochrome C can be significantly reduced by iron deficiency. Schultze [40] noted impaired formation and maintenance of cytochrome oxidase in copper deficiency. If such

changes in enzyme levels lead to disablement of the normal mechanisms of cell respiration, it is conceivable that adaptation occurs which is associated with malignant change. This general theory conforms to that advanced by Warburg,[41] and finds support in the observations of Greenstein and Meister [42] that the cytochrome oxidase concentration of neoplastic tissue is low, and these authors believe that a fair correlation exists between degree of malignancy and oxidative response. Weisberger [43] has also recently commented upon metabolic studies which "suggest abnormal patterns of oxidative mechanism" in "precancerous" leukoplakic tissue from the mouth. However, no cause-and-effect relationship has been proved.

The known interrelationships between copper and iron metabolism and their relationship to hematopoiesis suggest that the role of the trace metals in the etiology of the iron-deficiency state, the superimposed atrophic mucosal changes and the tendency to ultimate malignant change in Plummer-Vinson syndrome would be worthy of further investigation.

Preventive Measures: The precise etiology of Plummer-Vinson syndrome must still be considered to be uncertain, although the essential role of an iron-deficiency state seems highly probable. Preventive measures are, however, possible in such circumstances, as was classically demonstrated by Lind in the case of scurvy. There is evidence that the diets eaten by the present study groups today are considerably more adequate than were available to them in their youth, when the foundations of their disease state were laid. Since 1938 the Swedish Public Health Service has sponsored the fortification of white flour with iron and some of the B vitamins. Concomitantly, it is a widely held clinical impression in Sweden that Plummer-Vinson syndrome is becoming a progressively rarer entity, although, of course, the backlog of chronically irreversible cases will remain for many years. It seems highly likely that such steps to improve the dietary intake in this area also constitute a forward step in the control of hypopharyngeal cancer. While this process is in hand there would seem to be interesting possibilities in further studies of the basic mechanisms of Plummer-Vinson syndrome, with particular reference to its premalignant potentiality, the results of which might bear upon the general nature of malignant change in cells.

Summary and Conclusions

1. The present study is based upon 150 patients with dysphagia believed to be on the basis of tissue abnormalities associated with Plummer-Vinson syndrome. Statistical comparison is made with suitable control groups.

2. The distribution of Plummer-Vinson syndrome in Sweden has been reviewed and found to be most common in the northern rural areas.

3. Plummer-Vinson syndrome occurs in men, though relatively rarely, and a representative case is described.

4. The relative distribution of signs and symptoms is presented. Among these, early edentia has been relatively little stressed in previous reports.

Among 133 female Plummer-Vinson cases, 20 had lost their teeth prior to the age of 30.

5. Among the general medical disorders found to be more common among the Plummer-Vinson group are dry skin and hoarseness.

6. Menstrual flow was found to be somewhat heavier in the Plummer-Vinson cases than in the control cases. No differences were found in the number of pregnancies and the number of siblings between the study and the control cases.

7. The dietary pattern of the study and control cases is presented in some detail. The diet of the general population in which Plummer-Vinson disease occurs most commonly is deficient in fresh fruits, vegetables and meats.

8. Normal serum iron and hemoglobin do not rule out the presence of Plummer-Vinson disease. Sixty-eight per cent of 109 female patients had normal serum iron levels.

9. Cancer of the upper respiratory tract, and particularly cancer of the lower hypopharynx, are frequently closely related to the Plummer-Vinson syndrome.

10. A schematic diagram is presented indicating known and theoretic steps believed to be precursors to the Plummer-Vinson syndrome. Though chronic iron deficiency is thought to be a primary cause of this syndrome, it is suggested that other nutritional factors may be involved, although these have not been identified.

11. The apparent reduction in the present incidence of Plummer-Vinson disease suggests that nutritional supplements, perhaps of iron and vitamins B and C, are effective prophylactic agents both for the syndrome itself and for the types of cancer associated with it.

Summario in Interlingua

Le presente studio es basate super datos ab 150 patientes con dysphagia interpretate como associate con syndrome de Plummer-Vinson e ab varie gruppos de controlo requirite pro le comparation statistic. Es presentate un revista del distribution del syndrome de Plummer-Vinson in Sveda. Le revista monstra que le syndrome es le plus commun in le areas rural al nord del pais. Le distribution relative del signos e symptomas es presentate. Inter 133 femininas con syndrome de Plummer-Vinson, 20 habeva perdite lor dentes ante le etate de 30 annos. Le disordines medical general que es prevalente in iste gruppo es pelle sic e raucitate vocal. Le fluxo menstrual esseva un pauco plus intense in le casos del syndrome de Plummer-Vinson que in le casos de controlo. Nulle differentias esseva constatate inter le patientes e le gruppos de controlo con respecto al numero de pregnantias e al numero de fraternos. Le normas dietari in le gruppo del patientes e in casos de controlo es presentate in detalio. Es constatate que le dieta in le population general in que le morbo de Plummer-Vinson occurre es le plus communmente deficiente in fructos, vegetales, e carne fresc. Le presentia de normal ferro seral non garanti le absentia de morbo de Plummer-Vinson. Sexanta-octo pro cento del patientes feminin esseva normal in iste respecto. Nos ha notate que cancere del vias supero-respiratori e specialmente cancere del hypopharynge inferior es intimemente relationate con syndrome de Plummer-Vinson in un alte procentage del casos.

Es presentate un diagramma schematic que indica le cognoscite e le theoric stadios considerate como precursores del syndrome de Plummer-Vinson. Ben que un carentia chronic de ferro es reguardate como un causa primari de iste syndrome, le possibilitate es signalate que altere factores dietari participa in le etiologia de illo. Nulle tal ha usque nunc essite identificate. Le apparente regression currente in le incidentia del syndrome de Plummer-Vinson suggere que supplementos dietari—possibilemente ferro e le vitaminas B e C—es efficace agentes prophylactic, tanto pro le syndrome mesme como etiam pro le typos de cancere con que illo is associate.

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THERAPEUTICALLY "REFRACTORY" HYPERTENSION: CAUSATIVE FACTORS, AND MEDICAL MANAGEMENT WITH CHLOROTHIAZIDE AND OTHER AGENTS *

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Introduction

Although the great majority of hypertensive patients can be managed effectively with presently established medical programs,[1, 2] instances of failure to respond to treatment in a completely satisfactory manner are not uncommon. In our experience, such patients may include as many as 10% or more of the hypertensive population.[3] Major reasons for such "refractoriness" are probably at least twofold: (1) predisposition to intolerance of drug side-effects that prevents use of antihypertensive agents in adequate amounts, and (2) perhaps a more fixed or resistant type of blood pressure elevation that is not amenable to the therapy employed. Within the last year a new substance, chlorothiazide, has been found to be of value in the treatment of hypertension.[4, 5, 6, 7, 8] With the patient under careful electrolyte follow-up and replacement if necessary, this substance seems to be relatively nontoxic and to offer a definite advance in the control of hypertensive patients. Because it potentiates the hypotensive response to several medications,[6, 7, 8] we decided upon a trial of it as an adjunct to other materials in hypertensive subjects refractory to management. Such patients were selected from the clinic population, and chlorothiazide was therefore given along with agents that in each case had previously proved to be unsatisfactory. The latter were employed at doses generally well below those used beforehand. A large number of the patients thus treated had a very significant blood pressure reduction, and frequently an impressive improvement without troublesome side-effects.

Methods

Patients were selected from the hypertension clinic who had shown a lack of hypotensive response and an absence of significant symptomatic improvement with various drug therapies. Average follow-up was three and one-half years. The data were collected on blood pressure, heart, fundi and

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symptoms, if any, over three distinct periods: (1) prior to any therapy, (2) during the subsequent course on the particular drug, including the last program (if more than one had been tried) which had proved to be unsuccessful, and (3) following chlorothiazide treatment for two to five months. When feasible, base line electrolytes were determined and chlorothiazide was then given with one of the agents previously tried. Dosage initially was 250 mg. four times daily, changed shortly after the start of the study of 500 mg. twice daily in most instances. Average daily amounts of other agents used

SYMPTOMS FROM THE DISEASE	DATE	DATE	DATE	DATE
Headache				
Dizziness				
Urinary Symptoms				
Heart Failure				
Visual Disturbances				
Nervousness				
Chest Pain				
Other				
SIDE EFFECTS OF DRUGS				
Nasal Congestion				
Sleepiness				
Depression				
Edema				
Pounding Heart				
G. I. Trouble				
Weakness				
Hunger				
Other				
PHYSICAL EXAMINATION				
Weight				
Adhering to Medication				
B. P. 0 time				
5 minutes				
10 minutes				
B. P. Standing				
Pulse Rate (irregular?)				
Fundal Grade				
Heart				
Lungs				
Extremities				
Additional				

CHART 1. Follow-up check sheet used at each clinic visit.

were: reserpine, 0.25 to 0.5 mg., and reserpine-hydralazine combinations at 0.75 mg. and 150 to 400 mg., respectively. Five patients also received blocking drugs in various amounts. Blood pressures were recorded in the right arm with the patient reclining, at zero time and again at intervals of five and 10 minutes. Averages were determined for at least a total of six readings (at least two visits) in the pretreatment, the pre-chlorothiazide, and the chlorothiazide periods (table 2). Serum electrolyte levels were obtained in most cases after chlorothiazide therapy had been in progress for from two to five weeks for follow-up determinations. Orange juice, two to three glasses daily, or potassium chloride, 3 gm. daily, was given in five instances to prevent possible troublesome hypopotassemia or chloride loss. The first clinic revisit post-chlorothiazide therapy was at one week, with

TABLE 1

Reasons for Failure of Medical Therapy in 35 Cases

Side-Effects	Reserpine (Nine Cases)	Reserpine and Hydralazine (21 Cases)	Combination with Blocking Drugs (Five Cases)
Headache	1	6	None
Nasal congestion	3	9	None
Edema	2	4	None
Dyspnea	1	None	None
Depression	5	6	None
Weakness	1	None	2
Sleepiness	2	1	None
Gastrointestinal	1	1	3
Tachycardia	None	5	None
Dermatitis	None	1	None
Asthma	None	1	None
Nervousness	None	1	None
Dizziness	None	None	2
"Fixed hypertension" (side-effects not present)	2	3	2

subsequent studies at two- to three-week intervals. At each, a history and physical examination were carried out and notes taken on certain symptoms and organ systems, using specific "check list" follow-up records (chart 1).

RESULTS

1. *Causes of "Refractory Hypertension":* Of the 35 cases, unsatisfactory responses occurred to reserpine (nine), reserpine and hydralazine (21), and the latter two drugs in combination with one of the "autonomic blocking" drugs (five). No other medications were used. Review of the data demonstrated in general that the development of intolerable side-effects (of various types) was the most common cause of therapeutic failure (table 1). Twenty-eight patients considered themselves to be unable to continue on adequate dosage of the agents selected. Seven other patients were

maintained for from five to eight months on levels of these substances considerably higher than those found adequate in this clinic, without troublesome side-effects and yet with no acceptable change in blood pressure (table 1). These cases in particular manifested no detectable clinical differences from the large number that had responded favorably to these same medications.

2. *Chlorothiazide Therapy:* In comparison to the prominent side-effects, and a lack of a significant hypotensive action of the last therapy program given these patients prior to chlorothiazide, treatment with this drug and

TABLE 2

Summary of Data on 35 Cases of "Refractory" Hypertensive Disease

Mean B.P. Before any Therapy	Mean B.P. After Drug Therapy Prior to Chlorothiazide	Causes of "Refractoriness"		Mean B.P. After Chlorothiazide
		Side-Effects	"Resistant" B.P.	
212/126	236/121 5.8*/2.0*	28	7	169/97 4.8*/3.1*

* Standard error of mean.

the previously unsuccessful agent(s) was followed in the majority of instances by an impressive reduction in blood pressure (table 2), without complaints. This became apparent often after only six to seven days of chlorothiazide therapy. Thirteen cases showed a fall in blood pressure from significantly elevated levels ($> 200/110$) to values that were readily considered as normal ($< 150/90$). Four of these patients had been followed previously for over eight years without blood pressure changes and are now

TABLE 3

Cases of "Resistant Hypertension"

Comment	Response to Chlorothiazide
R.—B.P. responded to drugs with Ecolid, but not normal	210/120–170/100
Ma.—No side-effects to reserpine, Apresoline and Ecolid	210/110–130/60
Hr.—No side-effects to reserpine	220/134–170/98
Pa.—No side-effects to reserpine-hydralazine	220/120–130/80
Ru.—No side-effects to reserpine-hydralazine	220/120–190/95
Gr.—No side-effects to Apresoline-Ecolid	190/148–190/110–170/90
Fa.—No side-effects to reserpine-hydralazine	190/120–195/95

normotensive. All of the seven patients previously not responsive, yet without side reactions, showed acceptable blood pressure reductions when chlorothiazide was included with their medications (table 3). Loss of from 1 to 3 kg. in body weight was common; there was no close relationship, however, between the hypotensive response and either weight reduction or noticed diuresis. In fact, two cases showed a prominent blood pressure fall associated with moderate weight again. Two other subjects with advanced hypertensive heart disease and cardiac decompensation even while receiving digitoxin noticed complete disappearance of exertional dyspnea and or-

TABLE 4

Drugs Found to Be Effective with Chlorothiazide, Contrasted to Unsuccessful Prior Therapy*

Prior Treatment.....	Reserpine	Reserpine and Hydralazine	Blocking Drugs and Others in Combination
	9	21	5
Subsequent Adjunctive			
None	0	4	1
Reserpine	9†	11	1
Hydralazine		1	1
Reserpine and hydralazine		5†	1
Blocking drugs and others in combination			1†

* Five cases of the 35 seemed to have adequate response to chlorothiazide alone.
† Almost routinely, at much reduced doses.

thopnea, and the glycoside was successfully discontinued. The need for a pharmacologic agent in conjunction with chlorothiazide in most patients has been emphasized.[4, 8] For that reason, no attempt was made here to determine the hypotensive value of chlorothiazide alone in these refractory subjects. However, in five instances where chlorothiazide was given with other agents and the latter drugs were omitted, blood pressure reduction has continued. In addition, it was frequently possible, when chlorothiazide was used, to employ pharmacologic agents usually considered to be of lower potency than those previously not of benefit (table 4).

Three cases showed no definite improvement symptomatically and no significant reduction in blood pressure (< 30 mm. systolic and < 20 mm.

TABLE 5

Cases Unsuccessfully Treated with Chlorothiazide

Patient	Drugs Used with Chlorothiazide	Reasons for Failure
Ra.*	Reserpine-hydralazine	Developed auricular fibrillation
Ru.	Reserpine-hydralazine	An asthmatic; symptoms persisted, preventing higher doses of reserpine and hydralazine
Ma.	Reserpine	Unknown. No side-effects
Ia.	Reserpine-hydralazine	Developed prominent ventricular premature contractions (VPCs)
Fi.	Reserpine	Unknown. No side-effects
Gu.*	None	Developed prominent VPCs
Ro.†	Reserpine-hydralazine and Inversine	No change in supine B.P., but developed very adequate orthostatic response only after chlorothiazide was added to the regimen
Sa.*	Reserpine-hydralazine and Inversine	Developed gross hematuria and petechiae, thought possibly to be due to chlorothiazide
Wo.‡	Reserpine	Numerous petechiae on two occasions following chlorothiazide

* Satisfactory hypotensive response.
† Gastrointestinal effects controlled by smaller, more frequent doses, antacids and, in some cases, by lowering chlorothiazide dosage.
‡ Not included in series of 35.

diastolic) when chlorothiazide was added to a therapeutic regimen that previously was not beneficial (patients Ru., Ma. and Fi., table 5). A review of the clinical features of these cases failed to uncover any significant clinical differences between them and those subjects showing a prominent response. This group of patients is of considerable interest, however, for the failure of chlorothiazide to result in benefit, in contrast to its usual action, possibly indicates that this still "refractory" group may be different physiologically from the balance of the clinic population.

Side-Effects

Although side-effects have been described, chlorothiazide reputedly is a relatively nontoxic drug.[6, 7] In our experience this is generally true, but at least three and possibly four different types of symptoms were encountered that were thought to be the result of this drug.

1. *Gastrointestinal:* Seven cases showed significant gastrointestinal disturbances that required either cessation of the medication or a reduction in dosage by at least 50%. Nausea, epigastric distress, abdominal cramps and vomiting were the most frequent in this group. In all instances, when chlorothiazide was stopped and the other medications (reserpine, Apresoline and blocking drugs) were continued, the gastrointestinal manifestations promptly subsided. A reinstitution of chlorothiazide therapy at lower dosage levels was accompanied by a return of their epigastric discomfort to a mild degree, with definite benefit noted by antacids and antispasmodic therapy. This side-effect has been noted by others.[6, 7]

2. *Cardiac:* Four of the subjects who were receiving a digitalis drug because of previous cardiac decompensation developed irregularity of the pulse within three to eight days after chlorothiazide was started. In two the irregularity was thought to be frequent ventricular premature contractions (no electrocardiogram available). Multiple foci of frequent ventricular premature contractions in a third case and auricular fibrillation in a fourth were confirmed by electrocardiograms. In each, irregularity of the pulse ceased within four to 14 days after stopping chlorothiazide treatment. Although it was not possible to obtain electrolyte studies in these cases at the time, it was thought that the various irregularities of pulse may have resulted from potassium depletion in the myocardium with an increased myocardial irritability, a manifestation of the action of both digitalis and chlorothiazide.

3. *Hemorrhagic:* A patient with malignant hypertension developed gross hematuria and petechiae eight days after chlorothiazide therapy was begun. When chlorothiazide was discontinued the petechiae disappeared within seven to eight days, but the hematuria persisted for over three weeks. Two other subjects (not included in this series) while receiving chlorothiazide also developed hemorrhagic phenomena not previously present. One subject suffered severe melena, with nausea and vomiting; this patient had

previously been on reserpine and Apresoline without difficulty, and chlorothiazide had been added to her therapy eight days previous to the above-mentioned symptoms. All medication was stopped and her symptoms subsided in six to seven days, with return of normal stools. It was not definite that the melena was related directly to chlorothiazide, but this was a strong possibility. A second case * developed prominent petechiae over the lower half of the body within 10 days of the start of chlorothiazide therapy on two separate occasions (table 5). In each instance, stopping chlorothiazide was followed by a prompt disappearance of her petechiae (within eight to 12 days). In the second episode, this patient also developed microscopic hematuria at the time of petechiae formation which disappeared at an interval coinciding in general with cessation of petechiae formation.

4. *Central Nervous System:* Chlorothiazide produces a hypochloremic alkalosis.[9] In patients with epilepsy or seizure disorders, it is believed that alkalosis may predispose to the onset of convulsions. We have only one epileptic with hypertension in the clinic. Within four weeks after the start of chlorothiazide therapy she experienced three seizures; previously, over a period of five months she had had but one. Although this is not clearly the result of chlorothiazide, the agent was discontinued and the patient has subsequently been well.

Discussion

The frequent and sometimes profound hypotensive response to chlorothiazide combination therapy in patients who previously had been "refractory" to pharmacologic management has been impressive. Several subjects are now normotensive for the first time in many years of direct follow-up. The means by which chlorothiazide reduces blood pressure is not clear. Sodium depletion may be one of the important factors, but others seem likely as additional data accumulate.[9, 10] In several of our cases, reduction in blood pressure was not associated with either a definite diuresis or weight loss. Three subjects showed substantial hypotension with slight weight gain. Either the sodium loss in such cases was incipient, if the natruretic action of chlorothiazide is responsible for its hypotensive effect, or the sodium ion may in some way have been inactivated or trapped and been prevented from exerting its hypothetically sensitizing action on the contractility of arteriolar smooth muscle cells.

The need for careful electrolyte follow-up and control of patients receiving chlorothiazide, plus the occasionally not inconsiderable side-effects, suggest that it is not the first treatment of choice in the management of hypertension. The usually less troublesome symptoms produced by reserpine and hydralazine, and the frequent response to them, indicate that they are the primary agents to be tried. Failure to obtain suitable benefit should in most cases then be followed by chlorothiazide in combination with

* Courtesy of Dr. Harold Wainerdi.

one or both substances. If additional treatment is necessary, the fourth line of attack should include autonomic blocking agents added to less vigorous pharmacologic agents and chlorothiazide. Thus this drug, in our thinking, seems to belong between hydralazine and the blocking drugs in the "therapeutic spectrum" of hypertensive disease. It has increased the usefulness of other antihypertensives in our experience, and has a direct action of significant benefit on cardiac failure in hypertension.

The mechanism of the side-effects is completely unknown. The gastrointestinal reactions may be the result of direct irritation (electrolyte abnormalities were not present). The petechiae formation in at least two of the cases described above was associated with no demonstrable defect in the blood clotting mechanism. A direct influence on capillary fragility may be present (tourniquet tests were strongly positive), although an effect on other or unknown hemostatic factors is possible.

Conclusions

1. Thirty-five cases of refractory hypertensive disease were treated with chlorothiazide in addition to therapeutic regimens previously shown to be ineffective. The majority of cases showed a definite and impressive hypotensive response. The mechanism of action of this drug in such instances was not clear, but in some patients the absence of weight loss or diuresis suggests that its mechanism may not be entirely that of electrolyte loss.

2. Side-effects of these drugs, particularly gastrointestinal and hemorrhagic, are potentially distressing. Careful electrolyte follow-up should be provided.

3. The place of chlorothiazide in the therapy spectrum of hypertensive disease probably lies between reserpine, hydralazine and others, and the autonomic blocking drugs. If the first agents are not effective, chlorothiazide may be added to attempt to potentiate their effectiveness, prior to the use of the autonomic blocking drugs superimposed on a chlorothiazide-drug combination, if necessary.

Summario in Interlingua

Adverse effectos lateral e, in casos sporadic, un "hypertension fixe" pote devenir un serie obstruction del tractamento medical de morbo hypertensive. Inter le visitante patientes del Clinica pro Hypertension al Hospital New York, 35 patientes esseva seligite qui non habeva respondite a un previe tractamento con drogas a causa del un o del altere tal factor.

Omne iste patientes esseva retractate con le droga o combination de drogas que se habeva monstrate non-satisfactori. Le agentes usate esseva reserpina, hydralazina, e (in cinque casos) le un o le altere del drogas de blocage autonome. Chlorothiazido—in doses de 250 mg, quatro vices per die—esseva addite al regime que previemente habeva essite sin valor. Omne le patientes, excepte tres, monstrava promittente reductiones del pression de sanguine (plus que 30 mm systolic e plus que 20 mm diastolic). Dece-tres patientes ha attingite un stato de normotensivitate pro le prime vice in plus que cinque annos de tractamento sub altere programmas therapeutic.

In plure casos in discompensation cardiac con edema peripheric, il esseva possibile discontinuar digitalis e permitter un uso plus liberal de sal in le dieta.

Effectos lateral de chlorothiazido esseva commun. Illos representava plure categorias. In un de istos, il habeva prominente difficultates gastro-intestinal, con nausea, crampos abdominal, e—a vices—vomito. Quatro altere subjectos, que recipeva digitalis, disveloppava irregularitates del frequentia del pulso intra tres a octo dies post le institution de chlorothiazido, de maniera que le administration del droga debeva esser interrumpite. Duo disveloppava diathese hemorrhagic, con hematuria e un occurrentia extense de petechias. In ambes, le tendentia sanguinatori dispareva intra un septimana post le termination del administrationes del droga. Un quarte categoria de adverse effectos lateral es illustrate per un caso de epilepsia idiopathic con frequente attaccos intra un periodo de quatro septimanas post le initiation de chlorothiazido. Previemente le patiente habeva essite sin symptomas durante plus que cinque menses. In le curso de cinque menses depost le interruption del medication, iste patiente ha de novo essite libere de convulsiones.

Le conclusion es que chlorothiazido pote esser recommendate in le tractamento de hypertension post que plus simple mesuras se ha monstrate inefficace. Alora illo pote esser usate como adjuncto de reserpina e altere drogas, ante le essayo possibile de agentes de blocage autonome. Meticulose observationes consecutori es necessari a causa del effectos lateral e a causa del possibilitate—documentate per altere autores—del disveloppamento de disturbationes del balancia electrolytic in le sero. Illo es un agente utile, nonobstante, quando illo es usate cautemente in casos refractori de morbo hypertensive.

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PRIMARY PULMONARY HYPERTENSION: REPORT OF SIX CASES AND REVIEW OF LITERATURE * †

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With few exceptions, the diagnosis of primary pulmonary hypertension was made only at necropsy prior to the introduction of cardiac catheterization. Pathologists referred to this condition as primary pulmonary arteriosclerosis,[1] right ventricular hypertrophy of unknown origin,[2] primary pulmonary vascular sclerosis,[3, 4] and obliterative pulmonary arteriosclerosis.[5] The disease was thought to be rare. In 1931 McCallum [5] reported only one instance of obliterative pulmonary arteriosclerosis in 12,000 autopsies. In 1954 Goodale and Thomas,[6] in 10,000 autopsies, found two cases which fulfilled their criteria for the diagnosis of primary pulmonary arteriosclerosis.

Clinical and pathologic studies of this disease with extensive reviews of the reported cases have been published in three papers.[3, 4, 7] In 1935 Brenner [3] stated that only 16 reported cases could be accepted as having primary pulmonary vascular sclerosis. Six years later Brill and Krygier [4] analyzed 20 cases on record, including most of those reviewed by Brenner, that were thought to fulfill the requirements for a diagnosis of primary pulmonary vascular sclerosis. A correct antemortem diagnosis was made in only two. In 1952 Parmley and Jones [7] summarized the clinical and pathologic findings in 31 cases of primary pulmonary arteriosclerosis reported up to 1950. They included 17 cases described by Brenner and by Brill and Krygier, 11 additional cases reported between 1927 and 1950, and three cases of their own.

Since then about 50 cases in adults have been reported,[8-26] largely due to new interest in cardiopulmonary hemodynamics stimulated by the widely used technic of right heart catheterization. In over three fourths of these cases, right heart catheterization was performed.

The purpose of this report is: (1) to record clinical and physiologic data from six cases of primary pulmonary hypertension, and the pathologic findings in three; (2) to summarize similar data from patients over age 12 reported in the literature between 1950 and 1957, and (3) to emphasize the features permitting antemortem diagnosis.

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Methods of Physiologic Study

Subdivisions of the lung volume were determined in three patients by the helium dilution method of Meneely and Kaltreider.[27] The predicted vital capacity and residual volume were calculated from the regression formula of Baldwin et al.[28] and that of maximal breathing capacity from the formula described by Motley.[29]

The technic of right heart catheterization has been recently summarized.[30] Cardiac output was determined by the direct Fick principle. Pulmonary artery wedge or pulmonary "capillary" pressure was measured in four patients according to the method described by Hellems et al.[31] The mean pulmonary artery, pulmonary "capillary" and systemic artery pressures were measured by planimetric integration. The oxygen saturation of the blood was determined by the manometric method of Van Slyke and Neill.

Pulmonary artery and "capillary" pressures were measured in one patient (H. F.) during exercise in the recumbent position. Tolazoline hydrochloride (Priscoline) and hexamethonium in indicated doses diluted in physiologic saline were given through the cardiac catheter into the pulmonary artery over 10 to 15 minutes to two patients in three determinations. Studies of blood flow, pressure and resistances were conducted during a control period and shortly following the injection of these agents.

Resistances in the systemic and pulmonary circuits, and left and right ventricular work against pressure, were calculated according to the formulas described by Gorlin et al.[32] Ventricular stroke work was obtained by dividing the total ventricular work by heart rate. Right ventricular function was studied by plotting stroke work against end-diastolic pressure, as suggested by Sarnoff and Burglund.[33]

The upper or lower limits of the pertinent hemodynamic determinants in our laboratory are as follows:

Upper Limit: Pulmonary artery mean pressure (PA_m) 20 mm. Hg
Pulmonary "capillary" mean pressure ("PC"$_m$) 12 mm. Hg
Right ventricular diastolic pressure (RV_d) 5 mm. Hg
Total pulmonary resistance (TPR) 250 dynes-sec.-cm.$^{-5}$
Pulmonary vascular resistance (PVR) 150 dynes-sec./cm.^{5}
Right ventricular work: total 0.8 KgM/M^2/min.
stroke 10 GmM/M^2/beat
Arteriovenous oxygen difference (AV O_2 diff.) 48 c.c./L.

Lower Limit: Cardiac index (C.I.) 2.8 L/M^2/min.
Stroke index (S.I.) 35 c.c./M^2/beat

The variations of the hemodynamic determinants in two successive control measurements were presented in detail in a previous paper.[34] Follow-

ing the administration of a pharmacologic agent, any changes beyond these ranges were considered to be significant.

Cine-angiocardiograms were made in two patients according to the technic described by Watson and co-workers.[35]

Results

All six of our patients were women. Their ages ranged between 19 and 51 years. Three had had symptoms for a year or less prior to study; the

Table 1

Symptoms, Physical Findings, Laboratory Data and Course in Six Patients with Primary Pulmonary Hypertension

Patients Age and Sex	H. F. 32, F.	S. De W. 19, F.	L. S. 51, F.	E. L. 50, F.	D. P. 42, F.	C. R. 53, F.
A. *Symptoms*						
Duration prior to study	11 mos.	5 mos.	11 mos.	8 yrs.	Many years	10 yrs.
Exertional dyspnea	+	+	+	+	+	+
Fatigue	+	+	+	+	+	+
Palpitation	+	+	+	+	0	+
Syncope	+	+	0	0	0	0
Cough	0	0	0	+	0	0
Hemoptysis	0	0	0	0	+	0
Edema	+	+	+	+	0	0
Abdominal swelling	0	+	0	+	0	0
B. *Physical findings*						
Cyanosis	0	0	0	+	+	0
Jugular venous distention	+	+	+	+	0	0
Loud and split P_2	+	+	+	+	+	+
Murmurs:						
Apical systolic	0	+	+	+	0	0
Pulmonary systolic	0	0	+	+	+	+
Tricuspid systolic	+	+	+	+	+	+
Pulmonary diastolic	0	0	0	0	+	0
Hepatomegaly	+	+	+	+	0	0
Left laryngeal nerve paralysis	0	0	0	0	+	0
C. *Laboratory data*						
(1) Radiology						
Enlarged right ventricle	+	+	+	+	+	+
Prominent pulmonary artery	+	+	+	+	+	+
Normal left atrium	+	+	+	+	+	+
(2) Electrocardiogram						
Sinus rhythm	+	+	+	+	+	+
Right axis deviation	+	+	+	+	+	0
Right ventricular hypertrophy	+	+	+	+	+	?
Prominent P wave	0	+	0	+	+	0
(3) Hemoglobin (gm.%)	12.7	12.9	14.5	18.2 to 14.8	12.7	14.7
(4) Circulation time (sec.)						
Decholin	29	—	—	36	—	—
Ether	12	—	—	—	—	—
D. *Course*	8 mos.*	12 mos.*	8 mos.*	12 mos.*	Alive, no failure	Alive, in failure

* Duration between the onset of right ventricular failure and death.

others had noticed symptoms for eight or more years. The pertinent clinical features are summarized in table 1.

Dyspnea and fatigue on exertion were presenting symptoms in all. Four patients noted palpitation, and two had recurrent syncope. Hemoptysis occurred in one patient, and hoarseness secondary to left recurrent laryngeal nerve palsy was seen in one patient also. None complained of chest pain. Right ventricular failure was present in four patients at the time of first examination. This was manifest by elevated venous pressure, hepatomegaly, ascites and peripheral edema.

The most consistent auscultatory sign was a loud, split-second pulmonic sound. Cardiac murmurs were present frequently but were nonspecific in nature. Four patients had a systolic murmur at the apex and the tricuspid

TABLE 2

Ventilatory Studies in Three Patients with Primary Pulmonary Hypertension

	H. F. 9/22/53		D. P. 5/31/55		D. P. 8/13/57		C. R. 6/15/56	
	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
Vital capacity	2.50 L.	83%	2.84 L.	99%	2.57 L.	96%	1.84 L.	70%
Residual volume	0.85 L.	141%	1.44 L.	169%	2.28 L.	286%	1.89 L.	160%
Total lung capacity	3.35 L.	93%	4.28 L.	115%	4.85 L.	139%	3.92 L.	103%
RV/TC (%)	25	20	34	23	47	23	48	31
Maximal breathing capacity (L./min.)	—		83 L.	95%	85 L.	101%	55 L.	57%
Air velocity index	—		0.95		1.05		0.70	
Timed vital capacity (% of total)								
1 sec.	—		—		77		75	
3 sec.	—		—		95		93	
Ventilation (L./M²/min.)	4.14		4.25		5.92		3.29	
O_2 consumption (c.c./M²/min.)	98		115		152		111	
Ventilatory equivalent	4.22		3.70		3.4		2.96	

area; two had murmurs of pulmonary insufficiency. Cyanosis was present in one individual who was not in failure at the time of study. Clubbing was not observed.

The electrocardiograms of these six patients are shown in figure 1. Right axis deviation and varying degrees of right ventricular hypertrophy were present in all but one (C. R.). Three demonstrated prominent P waves. All patients had sinus rhythm at the time of initial study. However, subsequent tracings in C. R. revealed atrial fibrillation, although clinically there was no evidence of either arteriosclerotic or rheumatic heart disease.

Fluoroscopy and roentgenograms of the chest uniformly disclosed enlargement of the right ventricle and dilatation of the main pulmonary artery

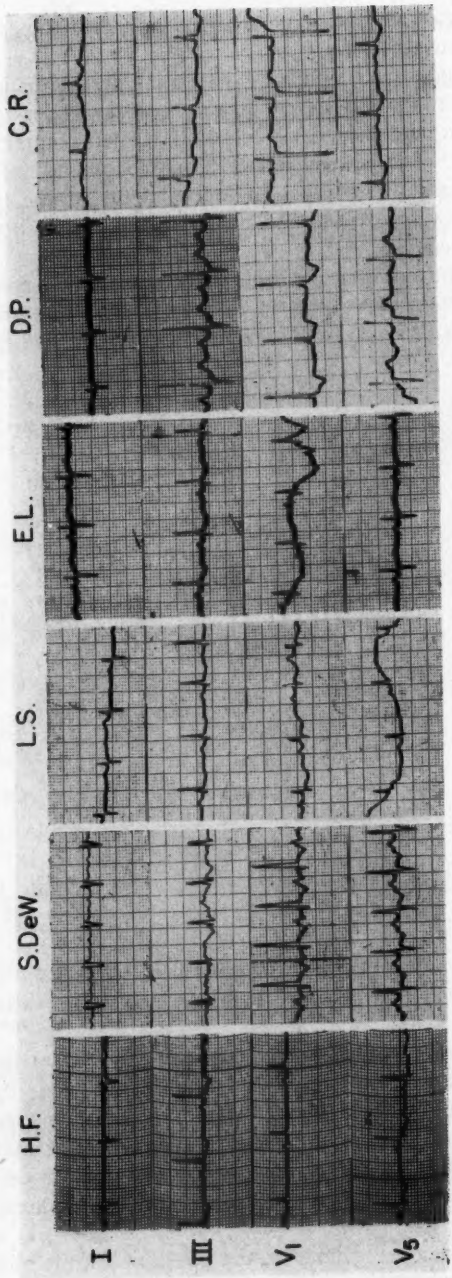

FIG. 1. Electrocardiograms of six patients with primary pulmonary hypertension.

TABLE 3

Hemodynamic Studies in Six Patients with Primary Pulmonary Hypertension

Case No.	Date of Study, BSA	Blood Flow						Pressures (mm. Hg)					Resistances (dynes-sec.-cm.$^{-5}$)			Ventricular Work Against Pressure (KgM/M^2/min.)	
		$\dot{V}_{O_2}$	A-V O_2 Diff.	C.I.	H.R.	S.I.	S_{aO_2}	PA (S/D M)	"PC" (M)	RV (S/D)	RA (M)	FA (S/D M)	TPR	PVR	TSR	Left	Right
1. H. F.	9/16/53 1.49	98	80.2	1.22	64	19	96	R 73/34 46 E 101/37 60	11 10	88/16 —	14 —	104/54 76 — —	2030 —	1650 —	3550 —	1.24 —	0.56 —
2. S. De W.	6/15/54 1.38	120	111.3	1.08	108	10	97	87/50 62	—	86/18	17	— —	3280	—	—	—	0.69
3. L. S.	5/24/55 1.72	110	80.5	1.37	100	14	90	70/38 48	6	70/14	13	139/92 108	1610	1440	3620	2.10	0.94
4. E. L.	3/18/55 1.77	121	96.9	1.25	100	13	93	100/40 56	—	94/13	13	— —	2060	—	—	—	0.79
5. D. P.	4/8/55 1.42	120	32.2	3.73	102	37	83	143/47 72	2	119/2	1	128/65 85	1080	930	1260	4.25	3.70
	12/13/55 1.42	116	30.0	3.87	100	39	85	158/50 77	6	126/4	4	113/55 78	1100	1020	1110	4.32	4.25
6. C.R.	5/26/56 1.72	120	51.7	2.32	70	33	92	89/41 59	2	89/3	2	135/63 88	1190	1150	1760	2.90	1.92
	10/1/57 1.66	124	72.1	1.72	82	21	87	— —	—	150/7	7	130/74 90	—	—	2320	2.21	—

BSA = body surface area (M^2)
$\dot{V}_{O_2}$ = oxygen consumption (c.c./M^2/min., STPD)
A-V O_2 Diff. = arteriovenous oxygen difference (c.c./L.)
C.I. = cardiac index (L/M^2/min.)
H.R. = heart rate (beats/min.)
S.I. = stroke index (c.c./M^2/min.)
S_{aO_2} = arterial blood oxygen saturation (%)
P.A. = pulmonary artery pressure
"PC" = pulmonary "capillary" or pulmonary artery wedge pressure
R.V. = right ventricular pressure
R.A. = right atrial pressure
F.A. = systemic artery pressure
S = systolic, D = diastolic, M = mean
R = rest, E = exercise
TPR = total pulmonary resistance
PVR = pulmonary vascular resistance
TSR = total systemic resistance

with increased hilar markings and clear peripheral pulmonary vascular shadows. In none was the left atrium enlarged. Increased pulsation of the left pulmonary artery was demonstrated in one patient (C. R.) in whom the possibility of an aneurysm of that artery was suspected.

Cine-angiocardiograms were obtained in two patients (L. S. and D. P.). In each case, enlargement of the right ventricle and delayed emptying of the dilated pulmonary arteries were demonstrated. The left heart and aorta appeared to be normal.

Table 2 summarizes pulmonary function studies in three patients. Except for a slight to moderate increase in the residual volume in two patients (D. P. and C. R.), and impairment of maximal breathing capacity in patient C. R., the findings were considered to be within normal limits.

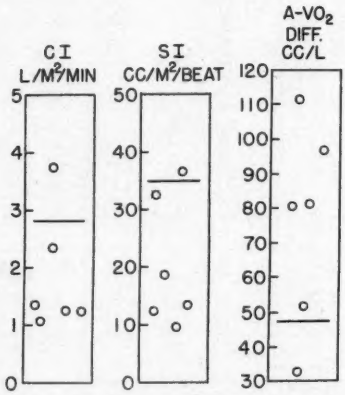

FIG. 2. Cardiac index, stroke index and arteriovenous difference in six patients with primary pulmonary hypertension. The horizontal bar in the first two boxes indicates the lower limits of normal, and that in the third box the upper limit of normal.

The hemodynamic studies in the six patients are presented in table 3 and in figures 2 to 4. Right heart catheterization was performed twice in two patients (D. P. and C. R.).

The cardiac and stroke indices were markedly decreased in four patients with right ventricular failure (H. F., S. De W., L. S. and E. L.), and normal in one patient (D. P.). In patient C. R. the cardiac index was slightly low during the first catheterization and was further reduced during the second. When the cardiac index was decreased, the A-V O_2 difference was increased.

The pulmonary artery pressure was uniformly elevated, and the mean artery pressure ranged from 48 to 77 mm. Hg. The pulmonary "capillary" pressure was recorded in four patients and was within normal limits in each. In two patients it was impossible to "wedge" the catheter. The pulmonary artery pressure of one patient (H. F.) increased further on exercise (PA

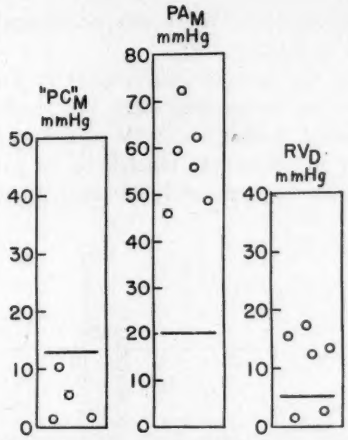

FIG. 3. Pulmonary "capillary" mean, pulmonary artery mean and right ventricular diastolic pressures in six patients with primary pulmonary hypertension. The horizontal bars in the boxes indicate upper limits of normal.

from 46 to 60 mm. Hg) without change in the pulmonary "capillary" pressure. The right ventricular systolic pressure of C. R. was much higher at the second cardiac catheterization, indicating probable progression of pulmonary hypertension. Unfortunately, the catheter could not be advanced through the pulmonary valve, so no comparison of the magnitude of the pulmonary hypertension could be made.

The right ventricular end-diastolic and right atrial mean pressures were elevated in four patients with clinical signs of right ventricular failure. The right ventricular diastolic pressure of C. R. was normal in 1956 and became slightly elevated in October, 1957, suggesting incipient right ventricular failure. Clinically, she has had corresponding symptoms and signs of de-

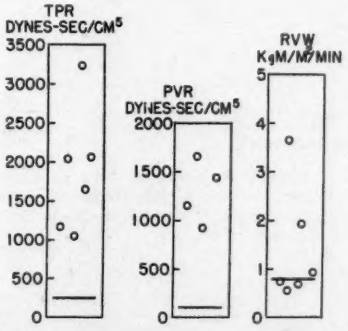

FIG. 4. Total pulmonary resistance, pulmonary vascular resistance and right ventricular work against pressure in six patients with primary pulmonary hypertension. The horizontal bars inside the boxes indicate upper limits of normal.

terioration. In patient D. P. there was no clinical or physiologic evidence of right ventricular failure.

Figure 5 shows the inverse relationship in these six patients between (1) cardiac and stroke indices and right ventricular diastolic pressure, and (2) cardiac and stroke indices and total pulmonary resistance.

Systemic artery pressure was normal in all patients, although systemic resistance was slightly to moderately elevated in two (H. F. and L. S.).

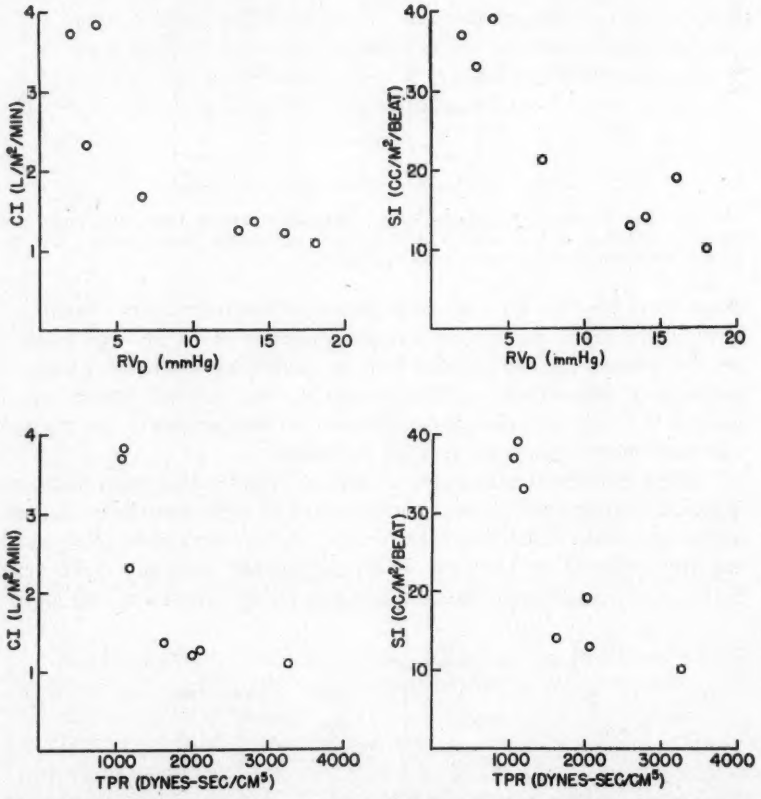

FIG. 5. *Upper half:* negative relationship between right ventricular diastolic pressure and blood flow, eight determinations in six patients. *Lower half:* negative relationship between total pulmonary resistance and blood flow, seven determinations in six patients with primary pulmonary hypertension.

Total pulmonary and pulmonary vascular resistances were markedly elevated, the former ranging from 1,080 to 3,280 dynes-sec./cm.^{5}, and the latter from 930 to 1,650 dynes-sec./cm.^{5} With normal pulmonary "capillary" pressure, the increased total pulmonary resistance is a reflection of increased pulmonary vascular resistance.

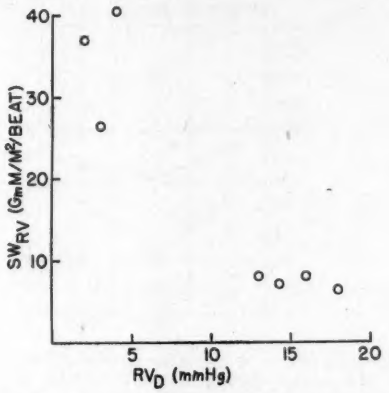

FIG. 6. Negative correlation between right ventricular stroke work and diastolic pressure in six patients with primary pulmonary hypertension. (Two determinations in patient D. P.).

Right ventricular work was increased fivefold in patient D. P., twofold in C. R., and was normal in the remaining four patients who had evidence of right ventricular failure. In figure 6, a negative correlation is shown between the stroke work and the diastolic pressure of the right ventricle.

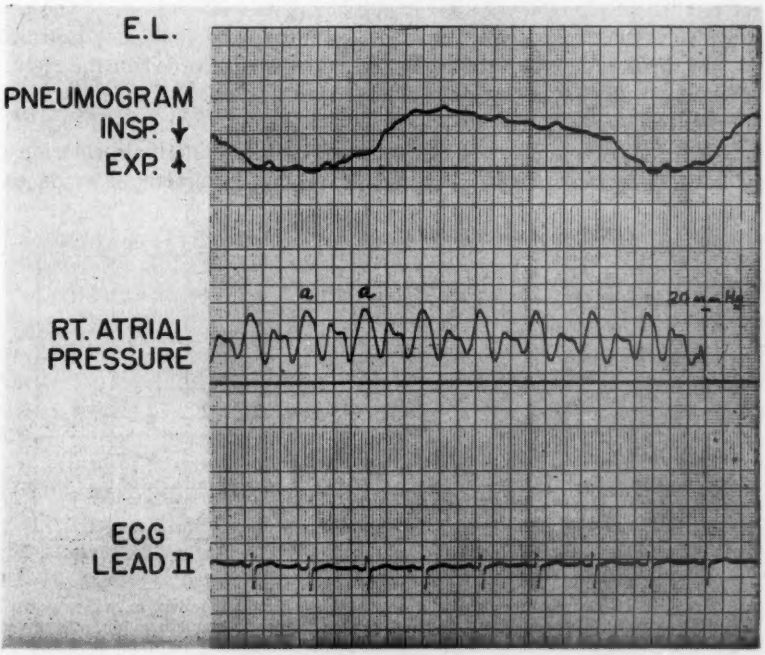

FIG. 7. Right atrial pressure with prominent "a" wave in patient E. L.

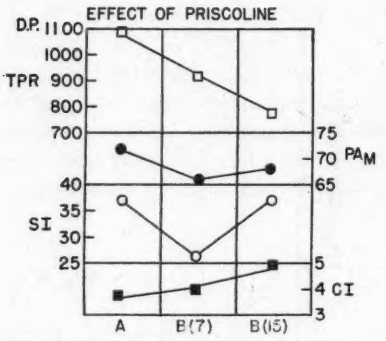

FIG. 8. Hemodynamic effects of tolazoline hydrochloride (Priscoline) in patient D. P. A = control period; B = period during which tolazoline hydrochloride was given. The figures in parentheses indicate minutes after the beginning of injection.

As the right ventricular filling pressure rose abnormally in the presence of failure, right ventricular stroke work against pressure actually declined.

There was no evidence in any patient of a left-to-right shunt in the heart or great vessels. The arterial blood oxygen saturation was 90% or higher in all but one patient (D. P.), whose saturation was 83% and 85% in two determinations. While she was breathing 100% oxygen, the amount of oxygen in physical solution in the blood was 1.3 vol. %. The presence of a valve-competent type of patent foramen ovale could not be ruled out.

In three patients a prominent "a" wave was recorded in the right atrial pressure tracing. A tracing obtained from patient E. L. is shown in figure 7.

The hemodynamic effects of intravenous tolazoline hydrochloride (Priscoline) on patient D. P., and of intravenous hexamethonium on patients

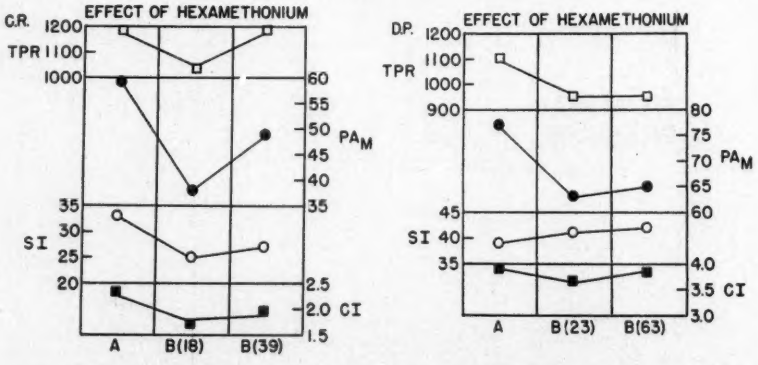

FIG. 9. Hemodynamic effects of intravenous hexamethonium in patients C. R. and D. P. A = control period; B = period during which hexamethonium was given. The figures in parentheses indicate minutes after the beginning of injection.

TABLE 4

The Effects of Intravenous Priscoline and Hexamethonium on Pulmonary Circulation in Primary Pulmonary Hypertension

Case	Date of Study	Periods of Study	Priscoline (mg.)	Blood Flow						Pressures (mm. Hg)				Resistances (dynes-sec./cm.^{5})		Ventricular Work Against Pressure (KgM/M^2/min.)	
				$\dot{V}_{O_2}$	A-V O_2 Diff.	C.I.	H.R.	S.I.	R.Q.	PA (S/D M)	"PC" (M)	FA (S/D M)		TPR	TSR	Left	Right
D. P.	4/8/55	A (7)	0	120	32.2	3.73	102	37	0.80	143/47 72	2	128/65 85		1080	1260	4.25	3.70
		B (15)	50	140	35.0	4.00	155	26	0.80	95/52 66	—	92/54 73		920	1020	3.87	3.65
			50	150	30.2	4.98	136	37	0.75	130/47 68	—	114/65 81		770	910	5.38	4.68
			C_4 (mg.)														
D. P.	12/13/55	A	0	116	30.0	3.87	100	39	0.86	158/50 77	6	113/55 78		1100	1110	4:32	4.25
		B (23)	6	129	35.8	3.67	90	41	0.74	128/41 63	—	95/45 59		950	890	3.08	3.28
		(63)	6	112	29.4	3.81	90	42	0.87	128/41 65	—	100/43 63		950	920	3.41	3.52
C. R.	5/25/56	A	0	120	51.7	2.32	70	33	0.82	92/38 59	2	135/63 88		1190	1760	2.90	1.92
		B (18)	6.5	106	61.2	1.73	70	25	0.90	60/30 38	—	84/47 59		1030	1600	1.32	0.79
		(39)	6.5	106	55.6	1.91	70	27	0.80	76/36 49	—	107/51 70		1190	1700	1.76	1.42

The abbreviations in this table are identical to those used in table 3.
A = Control period.
B = Period following Priscoline or hexamethonium (C_6) injection; the figures in the parentheses indicate the minute after the start of injection of either drug.

D. P. and C. R., are presented in table 4 and figures 8 and 9. Following injection of tolazoline hydrochloride, there was a decrease in pulmonary artery pressure and total pulmonary resistance, with some increase in the cardiac index. At the seventh minute following the injection, because of tachycardia, the stroke index was actually reduced. Intravenous hexamethonium reduced pulmonary artery pressure and pulmonary blood flow in both cases, but did not significantly affect the pulmonary vascular resistance. The reduction of pulmonary artery pressure was primarily a reflection of lowering of pulmonary blood flow, rather than vasodilatation.

FIG. 10. Photomicrograph of small pulmonary arteries in patient H. F. Note the advanced subendothelial (intimal) proliferation resulting in marked narrowing of the lumen. × 100.

Four of the six patients died within a year of the onset of right ventricular failure. Postmortem examination was performed on three patients (H. F., S. De W. and L. S.). None had a congenital malformation of the heart. Marked hypertrophy and dilatation of the right ventricle, and enlargement of the right atrium with variable pulmonary atherosclerosis, were present in all. Histologic changes in the small pulmonary arteries of the three patients are shown in figures 10, 11 and 12. In all, the lumina of the vessels were significantly reduced, either by extensive subendothelial (intimal) proliferation or by slight to moderate hypertrophy of the media.

There was no perivascular inflammatory change. In patient H. F., organized thrombi in many small arteries were observed.

Review of Literature and Discussion

Table 5 summarizes pertinent clinical and laboratory observations collected from the literature between 1950 and 1957 [8-26] in 55 patients over age 12 with primary pulmonary hypertension, in addition to those reported in the same period and analyzed by Parmley and Jones.[7] Because of the

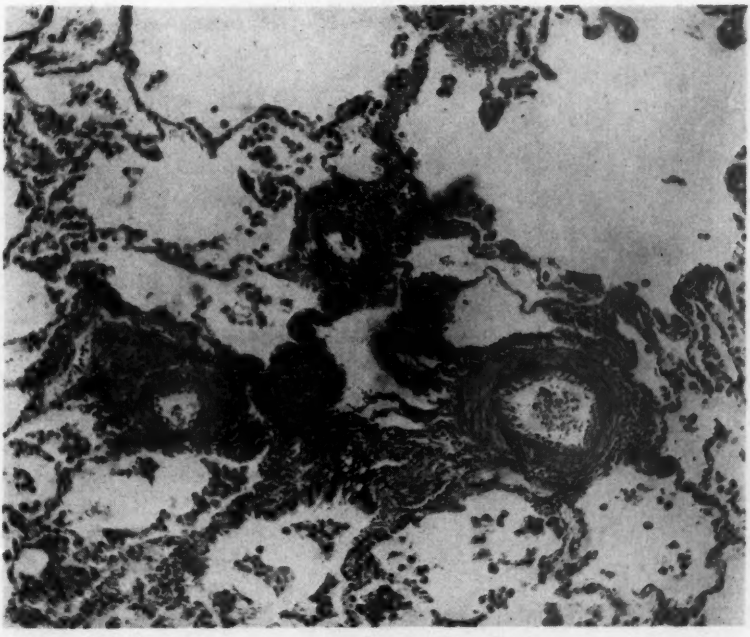

Fig. 11. Small pulmonary arteries in patient S. De W., exhibiting marked hypertrophy of the media and narrowing of lumen. × 100.

age of the patients, one case each was excluded from the series reported by Schafer,[20] Chapman [21] and Evans [24] and their respective associates. Only one of the three patients (case 1) studied by Dressler and his co-workers was included, as the other two cases were described in the paper by Dresdale and co-workers.[10] Only one of the seven patients (case 7) reported by Cutler and associates [17] was reviewed, because the other six patients had associated congenital cardiac lesions. This review did not include a total number of 18 children under age of 12 reported by Goodale and Thomas,[6] Wolman,[36] Berthrong and Cochran [37] and Carpenter and Pritchard.[38]

Primary pulmonary hypertension is usually seen in patients between 20

and 40 years of age, although it occurs in infants and children as well. The ratio of females to males over age of 12 is 4:1 among the reported cases; children under 12 are about equally distributed.

The most constant symptom was exertional dyspnea, apparently caused neither by pulmonary congestion nor by impairment of pulmonary function. It has been postulated that pulmonary hypertension per se might cause dyspnea by reflex stimulation of the respiratory center. Increased pulmonary vascular resistance with reduction of the pulmonary vascular bed may be another contributing factor. Syncopal attacks were present in more

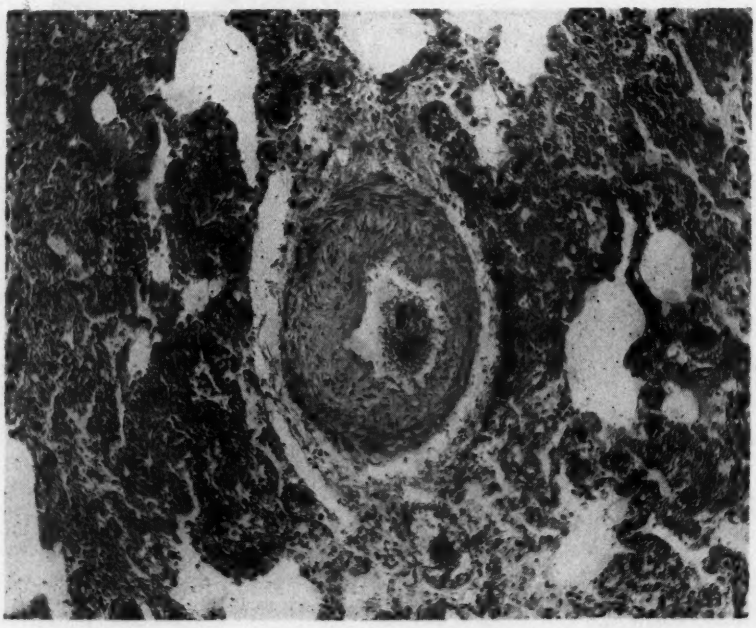

FIG. 12. Extensive subendothelial (intimal) proliferation of pulmonary arteries in patient L. S. The lumen of the vessel is moderately narrowed. × 100.

than half of the cases reviewed, usually precipitated by exertion. The mechanism of syncope is not clear, although it may be due to acute right ventricular failure with consequent cerebral anoxia.[15] Chest pain, frequently simulating angina pectoris, was present in about 40% of the cases reviewed. It may be directly attributed to severe pulmonary hypertension associated with dilatation and stretching of the pulmonary arteries.[39] Rarely were lesions of the coronary arteries demonstrated. Orthopnea was present in about 20% of cases, in most instances not associated with pulmonary congestion or edema. Cough and hemoptysis were mentioned in only 10% of the cases. Hoarseness caused by pressure on or paralysis of the left recurrent laryngeal

nerve by the enlarged pulmonary artery was present in four patients. In 40% of the cases reviewed, swelling of the legs occurred with or without abdominal distention. It usually indicated right ventricular failure.

Accentuation and splitting of the pulmonary second sound, and a right ventricular heave, were present, respectively, in over 90% and 70% of

TABLE 5

Summary of Clinical and Laboratory Findings in 55 Cases of Primary Pulmonary Hypertension Collected from the Literature Since 1950

	No. of Cases	%		No. of Cases	%
a. *Age and sex (55 cases)*			d. *Electrocardiogram (51 cases)*		
(1) Age			Sinus rhythm	47	92
12–20	9	16	Right ventricular hypertrophy	47	92
21–30	19	35			
31–40	20	36	e. *Roentgenogram (52 cases)*		
41–50	6	11	Right ventricular enlargement	48	92
over 50	1	2	Pulmonary artery dilatation	49	94
(2) Sex					
Male	11	20	f. *Cardiac Catheterization*		
Female	44	80	(1) C.I. (21 cases)		
			<2.8	20	95
b. *Symptoms (55 cases)*			>2.8	1	5
Exertional dyspnea	54	98	(2) PA_m (47 cases)		
Syncope	30	55	<40	2	4
Chest pain	23	42	40–80	28	60
Fatigue	21	38	>80	17	36
Swelling of legs	21	38	(3) "PC_m" (20 cases)		
Orthopnea	14	25	<12	17	85
Cough	10	18	>12	3	15
Hemoptysis	7	13	(4) S_{aO_2} (28 cases)		
Hoarseness	3	6	<85	7	25
			85–94	9	32
c. *Physical Signs (55 cases)*			>94	12	43
Accentuated P_2	49	89	(5) RV_d or RA_m (36 cases)		
Cardiac enlargement	40	73	<8	15	42
Right ventricular heave	34	62	>8	21	58
Cardiac murmurs:					
Apical systolic	25	45	g. *Pathologic Findings (41 cases)*		
Parasternal diastolic	14	25	Pulmonary atherosclerosis	37	90
Pulmonary systolic	17	31	Subendothelial or intimal thickening	36	88
Apical diastolic	3	6	Medial hypertrophy	32	78
Liver enlargement	28	51			
Cyanosis	25	45			
Edema	19	35			
Distended jugular veins	17	31			
Systemic hypertension	3	6			
Clubbing of fingers	3	6			
Gallop rhythm	3	6			

The abbreviations in this table are identical to those used in table 3.

The percentages in each category include only those cases in which the specific symptoms, signs and changes were mentioned. The remaining portion of 100% for each item includes those cases in which the specific item was either absent or not stated.

the cases reviewed. Cardiac murmurs were present irregularly and were nonspecific in character. An apical systolic murmur was heard in about half the patients. The same murmur was usually audible over the tricuspid area. A parasternal diastolic murmur indicating relative pulmonary in-

competence was heard in about 30% of the cases. In three patients a rumbling apical diastolic murmur was heard, but mitral stenosis was ruled out by postmortem examination. Cyanosis was described in more than 40% of the patients reviewed. In over one third of the cases, signs of right ventricular failure were present. Concomitant systemic hypertension and clubbing of the fingers were mentioned in three cases each.

The electrocardiograms showed sinus rhythm and right ventricular hypertrophy in over 90% of the cases reviewed. In most cases the electrical position was vertical, with right axis deviation. Radiologic examination disclosed cardiac enlargement, predominantly right ventricular, in 92% of the cases. In the left anterior oblique view, the left ventricle may overlap the spine due to posterior displacement by an enlarged right ventricle. The pulmonary artery and its major branches were uniformly enlarged, and in many instances the amplitude of pulsation was increased. In contradistinction, the peripheral lung fields were unusually clear, suggesting increased pulmonary vascular resistance and narrowing or obliteration of peripheral pulmonary vessels. The picture is characteristic of precapillary pulmonary hypertension as opposed to that seen in postcapillary pulmonary hypertension, in which some degree of pulmonary congestion is usually demonstrable.

Pulmonary function studies were carried out in only a small number of cases, and the findings were usually within normal limits or were only slightly abnormal. In none of these cases could the degree of pulmonary hypertension be explained by parenchymal disease of the lung.

Physiologic studies disclosed moderate to marked pulmonary hypertension, pulmonary artery mean pressure exceeding 40 mm. Hg in all but two patients. In patients whose pulmonary "capillary" pressure was measured, it was less than 12 mm. Hg (upper limit of normal) in all but three. In none of the three did the pulmonary "capillary" pressure exceed 14 mm. Hg. In 20 of the 21 cases where the cardiac index was measured, it was subnormal. Most of these had evidence of right ventricular failure. Total pulmonary and pulmonary vascular resistances were markedly increased in all patients, ranging from four to 14 times normal. Inasmuch as the pulmonary "capillary" pressure was normal in most cases, the increased resistance must occur between the pulmonary artery and pulmonary capillaries from organic and probably functional narrowing of small pulmonary arteries and arterioles. Physiologic evidence of right ventricular decompensation was present in about 60% of the 36 cases reviewed.

Patients with primary pulmonary hypertension may be separated into two physiologic groups: one including those patients with a compensated right ventricle, and one including those with a decompensated right ventricle. Patients of the first group usually exhibit lower pulmonary vascular resistance, higher cardiac output and increased right ventricular stroke work. On the other hand, patients in the second group usually have a higher pulmonary vascular resistance, lower cardiac output and subnormal right ven-

tricular stroke work. In these latter patients the increased filling pressures are probably a consequence of incomplete ventricular ejection and decreased myocardial contractility, resulting in a shift of the right ventricle from a normal function curve to a depressed one.[33]

Werko and associates [14] showed that exercise provoked a precipitous rise in pulmonary artery pressure in their patient, with no change in cardiac index or pulmonary capillary pressure. Thus it may be assumed that a rise in pulmonary vascular resistance occurred on exertion. As a consequence, acute right ventricular failure may occur with exercise in some patients.

Arterial oxygen desaturation was present in more than half the cases reviewed where the determination was made. The mechanism of arterial desaturation may be right-to-left shunt or impaired diffusion of oxygen.[40] In the absence of intracardiac shunt, breathing 100% oxygen usually raises the amount of oxygen in physical solution in the blood to 1.5 vol. % or higher.[41] The dilution technic described by Wood, Swan and associates [42] would be valuable in excluding the presence of small veno-arterial shunt in these patients.

The use of tolazine hydrochloride (Priscoline) has been advocated by Dresdale and his associates [11] in the study and management of patients with primary pulmonary hypertension. However, Rudolph and associates [43] observed that one of their patients with primary pulmonary hypertension failed to respond to the same drug. Shephard and co-workers [22] found that inhalation of 100% oxygen failed to reduce the pulmonary vascular resistance significantly in seven of their eight patients. Recent studies by Harris [44] showed significant reduction of the pulmonary artery pressure following acetylcholine injection in only one of three patients with primary pulmonary hypertension. From these observations and the results obtained in the patients of the present series, it would appear that the increased pulmonary resistance is due mainly to organic changes, although functional vasoconstriction may be a contributing factor, especially early in the disease.

The development of right ventricular failure in these patients is an ominous sign. Most patients died within two years of the onset of right ventricular failure. Sudden death was reported in several patients, and five patients died during or shortly following cardiac catheterization.

The pertinent pathologic findings were confined to the right side of the heart and pulmonary vascular system. The right ventricle was uniformly hypertrophied and dilated, and the right atrium was usually enlarged. The left side of the heart showed little or no abnormality. A patent foramen ovale was present in a small number of cases. The main pulmonary arteries were enlarged and atheromatous changes were observed in 90% of the cases. Histologically, subendothelial or intimal proliferation of small pulmonary arteries and arterioles was present in all but a few patients. Hypertrophy of the media was described in about 80% of the cases reviewed. Short and

associates [45] thought that the medial hypertrophy was actually a result of contracture of small arteries. This may explain why pulmonary vascular resistance was reduced in some cases following the administration of certain pharmacologic agents, presumably a result of vasodilatation. In all cases there was moderate to marked reduction in the lumina of the small vessels. Necrotizing angiitis was described in several cases.[12, 19, 22]

An unsettled problem is the nature of the thrombo-embolic changes in the lumina of the small pulmonary arteries. It is well known that repeated episodes of pulmonary thrombosis and embolism may lead to marked increase in pulmonary vascular resistance and pulmonary hypertension.[46] On the other hand, it is possible that long-standing pulmonary hypertension with weakening of the vessel wall may predispose to thrombo-embolism of the pulmonary vessels.

The pathogenesis of primary pulmonary hypertension is as mysterious as that of primary systemic hypertension. It may be due to persistence of the fetal anatomy of the pulmonary vessels, excessive pulmonary vasomotor tone, or other unknown factors. Some patients may have a marked increase in pulmonary vascular resistance and severe pulmonary hypertension during infancy and childhood and succumb rapidly to right ventricular failure. Others may have a relatively mild course before adolescence, but progress rapidly during the childbearing age. It is uncertain whether the aggravation is related to neurohormonal imbalance, producing increased pulmonary vasoconstriction or additional obstructive lesions in the pulmonary arteries as a result of repeated thrombo-embolic episodes. The association of Raynaud's disease in three patients with primary pulmonary hypertension has been offered as indirect evidence in support of a hyperactive neurohormonal vasomotor mechanism.[47]

The possibility of primary pulmonary hypertension should be suspected whenever the following features are present:

1. History of progressive exertional dyspnea, fatigue and repeated syncopal attacks.
2. Physical signs of pulmonary hypertension (right ventricular heave, and loud, often split and palpable pulmonary second sound), with nonspecific cardiac murmurs.
3. Electrocardiographic changes consistent with right ventricular hypertrophy.
4. Roentgenologic evidence of enlargement of right ventricle and pulmonary artery with normal left atrium and clear peripheral lung field.
5. Normal or slightly altered pulmonary function.
6. Marked pulmonary hypertension with normal pulmonary "capillary" pressure by right heart catheterization; absence of intracardiac shunt confirmed by catheterization and, if feasible, by dye dilution technic.
7. Rapidly downhill course following the development of right ventricular failure.

Thus, with all the above features, one can rule out with certainty pulmonary hypertension secondary to (1) mitral valvular disease, (2) left ventricular failure, (3) congenital malformation of the heart and great vessels, (4) extensive parenchymal disease of the lungs, and (5) severe pericardial, myocardial or endocardial disease.

An antemortem diagnosis of primary pulmonary hypertension was made in three patients of the present series (H. F., S. De W. and L. S.), and was subsequently confirmed by autopsy in all.

At the present time, no specific therapy is available for this condition. Oral Priscoline and Ansolysen were given to two patients, with inconclusive results. The response to sympathectomy and shunt operations by other workers has been disappointing.[14, 21] Because of the occasional tendency to spontaneous pulmonary thrombosis, the use of anticoagulant therapy may be considered.[21]

Summary

This report described clinical, physiologic and pathologic features of six patients with primary pulmonary hypertension.

Exertional dyspnea and fatigue were present in all. Less frequent symptoms included palpitation, syncope, cough, dizziness, cyanosis and hemoptysis. Cardiac murmurs were nonspecific. The second pulmonic sound was uniformly accentuated and often split.

The electrocardiogram showed right ventricular hypertrophy in five patients, and prominent P waves in three. Radiologic examination disclosed enlargement of the right ventricle and pulmonary artery and absence of left atrial enlargement in all patients. Minimal alteration in pulmonary function was observed in one patient.

Right heart catheterization revealed marked pulmonary hypertension with normal pulmonary "capillary" pressure, high pulmonary vascular resistance and low cardiac output in those patients with right ventricular failure. A negative correlation was observed between the stroke work and the filling pressure of the right ventricle.

Intravenous tolazine hydrochloride (Priscoline) and hexamethonium caused slight to moderate reduction in pulmonary vascular resistance.

Four patients developed right ventricular failure and died within one year of onset of failure. Pathologic examination in three patients demonstrated right ventricular hypertrophy and enlargement, right atrial enlargement and dilatation of pulmonary arteries with atheromatous changes. Histologic studies disclosed marked reduction in arterial and arteriolar lumina due to subendothelial (intimal) proliferation and medial hypertrophy.

Pharmacodynamic and histologic studies in the patients of the present series and those recently studied by other workers suggest that pulmonary hypertension in these patients is largely due to structural pulmonary vascular changes, and that functional pulmonary vasoconstriction plays a minor role.

A brief review was made of 55 cases of primary pulmonary hypertension collected from the literature during the period between 1950 to 1957. Their pertinent clinical, physiologic and pathologic features were summarized and discussed.

Diagnostic features of this disease were outlined and the feasibility of clinical diagnosis was emphasized.

Addendum

Since the submission of this manuscript, patient C. R. has died. The death occurred within one year of the onset of right ventricular failure. No postmortem examination was performed.

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Summario in Interlingua

Es presentate in detalio le observationes clinic e physiologic facite in sex patientes con primari hypertension pulmonar. Simile datos ab 55 casos trovate in le litteratura depost 1950 es summarisate.

Septanta pro cento del patientes habeva etates de inter 20 e 40 annos. Le proportion inter femininas e masculos esseva 4:1.

Le plus importante symptoma esseva dyspnea post effortio. Minus frequente esseva le symptomas de syncope, dolor thoracic, tumescentia del gambas, tusse, e hemoptysis.

Le plus frequente constatation physic esseva un accentuate e findite secunde sono pulmonar. Un murmure systolic apical esseva audite in circa un medietate del casos. Cyanose, un parasternal murmure diastolic, e signos de disfallimento dextero-ventricular esseva presente, cata un, in circa un tertio del casos.

Le electrocardiogramma monstrava, quasi in omne casos, rhythmo sinusal e alterationes compatibile con hypertrophia dextero-ventricular. Le examine radiologic revelava usualmente un allargamento predominantemente dextero-ventricular, prominente segmentos de arteria pulmonar, un clar campo pulmonar al peripheria, e normalitate del atrio sinistre. Studios ventilatori (in un micre numero de casos) esseva essentialmente normal.

Catheterismo dextero-cardiac indicava marcate grados de hypertension pulmonar con normal pression "capillar," alte resistentia pulmono-vascular, basse rendimento cardiac, e absentia de shunting intracardiac.

Es presentate un revista del alterationes hemodynamic observate post administration intravenose de hexamethonium, Priscolina, e acetylcholina, post exercitio, e post le inhalation de 100% de oxygeno. Es suggerite que augmentos del resistentia pulmonar resulta primarimente de alterationes del vasculatura pulmonar, ben que il es possibile que vasoconstriction functional constitue un factor contributori, specialmente durante le prime stadios del morbo.

Le majoritate del patientes moriva intra duo annos post le declaration del disfallimento dextero-ventricular. Le pertinente constatationes pathologic includeva marcate grados de hypertrophia dextero-ventricular, allargamento dextero-atrial, e

varie grados de atherosclerosis pulmonar. Le natura del phenomenos thromboembolic in le passages del micre arterias pulmonar non es cognoscite.

Es signalate que le totalitate del mentionate characteristicas clinic e laboratorial rende possibile le diagnose ante morte de primari hypertension. Isto es illustrate per le facto que le diagnose clinic esseva confirmate al necropsia in omne le tres patientes del presente serie in qui necropsias esseva effectuate.

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A STUDY OF VIRAL HEPATITIS IN A PENAL INSTITUTION*

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THE occurrence of viral hepatitis in institutions of various types is well known and has been reported previously.[1] The present report concerns a study of viral hepatitis in a penal institution carried out during an 11-month period. From the epidemiologic evidence obtained it is believed that parenteral transmission was of significance in the behavior of the disease during the period considered, and that the hepatitis was predominantly due to the serum (B) type rather than to the infectious (A) type. Since prison populations are not infrequently utilized as donor sources by agencies conducting blood-collection programs, it is important to consider this possibility.

DESCRIPTION OF THE INSTITUTION

The institution in which this study was conducted is a minimal-security prison located in the southeastern United States. The prison compound is made up of nine dormitories for the housing of inmates, a dining hall, an administration building, and service and recreational facilities. Surrounding are farm and pasture lands belonging to the institution where farming and dairying are carried on to help in the support of the institutional population.

The institution accommodates both white and Negro inmates. Census figures by race on October 19, 1955, showed 2,377 inmates in the institution, of whom 78.8% were white and 21.2% Negro. During the period 1950 to 1955, the inmate population has varied from 1,845 to 2,474. Data on percentage of white and Negro inmates for previous years are not available but are thought by prison officials to have been similar to those for the date given. Turnover in inmate population is rapid. From 1950 through 1955, the number discharged annually has varied from 54.1 to 62.3% of the prison population. This is largely accounted for by the fact that men receiving short sentences for the less serious crimes are usually interned here rather than in a maximal-security prison. There are, however, a number of inmates serving longer terms, ranging to life. Many inmates in the institution have served one or more previous sentences, but are not segregated from first offenders.

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On entry into the prison, inmates are placed in a quarantine facility located in one of the wings of the administration building, where they are isolated for a 21-day period. During this time the inmates are given psychologic tests for job and rehabilitation classification, a medical examination (including a chest x-ray), and are immunized against typhoid fever and tetanus. Because of personnel limitations, medical histories and immunizations are performed by inmates and are in general unsatisfactory. At the end of 21 days, new inmates are assigned to a dormitory and become part of the usual prison life.

Inmates are housed in nine dormitories which have been given numerical designations. Dormitories 1, 3, 4, 5, 6 and 9 are made up of four wings each. Each dormitory wing usually provides barrack-type accommodations for from 50 to 85 inmates. Only one wing of dormitory 7 is used for housing, the other three wings being occupied by school facilities. Dormitories 2 and 8 are made up of individual rooms occupied by one or two inmates. These rooms are usually assigned to inmates performing skilled or clerical work. Negro inmates are housed separately from white inmates in dormitories 5 and 6. For infraction of prison rules, the men may be placed in individual cells in a cell block in the administration building for such length of time as is deemed necessary.

From 6 a.m. to 5 p.m. the inmates are free to move at will within the prison compound. Those assigned to work details, both within the compound and outside, are usually supervised during this period by guards. The inmates who are unassigned may pass the day as they choose, with little direct supervision. During other hours the inmates are confined under lock to their dormitory wing.

All water used comes from an artificial lake and is treated by coagulation, rapid sand filtration, and chlorination before distribution. Routine testing has not demonstrated contamination. Sewage is handled by a central disposal plant, which is State-inspected and approved. Milk is obtained from the prison dairy, where it is pasteurized before use. Inmates eat in a common dining room in two successive shifts, except for those in the quarantine facilities, the cell blocks and the prison hospital. Prison officials and guards eat in a separate dining room but in the same building as the inmates. All food is prepared in a central kitchen by inmate cooks.

When ill, inmates are seen by the prison physician and, when necessary, may be hospitalized in the prison hospital. Nursing care is provided by other inmates who usually have had no previous hospital experience.

Viral Hepatitis in Previous Years

An estimate of the incidence of jaundice in the institution in the 10 years prior to the study was obtained by (1) review of hospital records for cases of jaundice, (2) a survey of card histories since 1949 of those inmates who volunteered as blood donors, (3) posting a notice on the prison bulletin

board requesting the names of inmates with a history of jaundice, and (4) questioning of known cases and other inmates who had been in the institution during this period about other possible cases.

From January 1, 1945, through July 31, 1955, 54 inmates were found who had a record of hospitalization for jaundice and/or a history of jaundice from two or more independent sources. These were designated as probable cases.

Table 1 presents the distribution of probable cases for this 10½ year period. It is seen that there was an increase in the number of cases beginning in 1954, and possibly in 1953. This may have been due to (1) an

TABLE 1

Probable Cases of Viral Hepatitis During the Period 1945 Through 1955

Year	Number of Cases
1945	1
1946	1
1947	0
1948	4
1949	4
1950	2
1951	0
1952	3
1953	5
1954	17
1955*	17
Total	54

* Seven-month period, January through July only.

increase in the incidence of the disease in the institution, or (2) the difficulty in case-finding for earlier years. Questioning of many inmates who had been in the institution during most of this period indicated that there probably were few cases prior to 1953, and this was confirmed by the prison guard who had been in charge of the hospital since 1947. It is believed, therefore, that the data are probably correct as a reflection of the amount of icteric hepatitis in the institution, and that there was a true increase in incidence.

METHOD OF STUDY

The study was carried out at the prison during an 11-month period from August, 1955, through June, 1956. All inmates having viral hepatitis were admitted to the prison hospital, where they were seen at least once by both investigators. A detailed clinical and epidemiologic history was elicited and a physical examination carried out. Testing for bilirubin in the urine was carried out by the prison technician, who was found to perform this determination reliably. Other laboratory tests were done at the Communicable Disease Center laboratories. Those who fulfilled three of the following four criteria were designated as cases: (1) a compatible history,

(2) icterus, (3) other signs on physical examination indicative of acute liver disease, and (4) compatible laboratory data. During the 11-month period, 50 patients were admitted to the prison hospital with the diagnosis of viral hepatitis. Of these, 45 fulfilled three of the criteria used and have been designated as confirmed cases.

TABLE 2

	No. of Cases	Per Cent
Symptoms		
Loss of appetite	43	96
Nausea	42	93
Dark urine	42	93
Lassitude	40	89
Vomiting	34	76
Abdominal discomfort	33	73
Light-colored stools	30	67
Pruritus	29	64
Weight loss	27	60
Constipation	23	51
Myalgia	23	51
Fever	19	42
Headache	19	42
Arthralgia	16	36
Sore throat	10	22
Cough	8	18
Coryza	5	11
Diarrhea	4	9
Signs		
Jaundice	39	87
Scleral only	18	40
Generalized	21	47
Hepatic tenderness	38	84
Enlarged and palpable liver	36	80
Spider angiomata	14	31
Palmar erythema	9	20
Palpable spleen	3	7
Lymphadenopathy	1	2

CLINICAL CHARACTERISTICS

Table 2 presents the frequency per cent of clinical symptoms and signs exhibited by the 45 patients fulfilling the definition adopted for a case. Twelve of the patients (36%) characterized the onset of their illness as abrupt, while 33 (64%) described it as gradual. A sense of depression, weakness, lassitude, anorexia described as an aversion to food, nausea and vomiting were the usual early symptoms. Upper respiratory symptoms, fever and diarrhea were uncommon. A 1 to 2° elevation in temperature was noted in seven patients upon admission to the prison hospital; fever above 101° was not found in this series of cases. The four patients who experienced mild diarrhea early in their illness became constipated with the onset of icterus.

Twenty-one patients developed generalized icterus, while in 18 patients icterus was confined to the sclerae. Thirty-two patients noticed the presence of icterus from one to 20 days after the onset of symptoms, while seven

patients (18% of those developing icterus) noticed icterus prior to or simultaneous with the onset of other symptoms.

Six cases were anicteric throughout the course of their illness and will be described briefly:

Case Reports

Case 4. Patient presented with a history of lassitude, headache, anorexia, nausea, vomiting, right upper quadrant pain, and weight loss of 25 pounds, these symptoms having been present for three weeks prior to the time of hospitalization. He reported dark urine, but had not noticed yellowishness of skin or eyes. Physical examination four days after hospitalization revealed a tender liver edge palpable 2 cm. below the costal margin. Spleen was not felt. Urine bilirubin at time of hospitalization was 4 plus; subsequent examination 13 days later was negative.

Case 7. Patient presented with a history of lassitude, anorexia, nausea, vomiting, and discomfort in the right upper quadrant of the abdomen for three days. He reported that his urine was dark in color. When examined on the seventh day of illness the liver could not be felt, and tenderness to palpation was not present in the right upper quadrant. However, shock over the right costal margin elicited definite pain. Urine bilirubin on the third day of illness was 2 plus; on the fifth day of illness, trace. No other laboratory data were obtained.

Case 29. Patient presented with a history of lassitude, headache, anorexia, nausea, right upper quadrant discomfort, and constipation of a week's duration. Physical examination on the seventh day of illness revealed a tender liver edge palpable 5 cm. below the costal margin and a palpable spleen. Urine bilirubin and cephalin flocculation on the thirteenth day of illness were both negative.

Case 36. Patient presented with a history of lassitude, anorexia, nausea, vomiting, abdominal discomfort, and dark urine for two days. Examination at the time of admission revealed a liver palpable 6 cm. below the costal margin, with tenderness to shock and palpation. Urine bilirubin was 2 plus. Symptoms subsided rapidly, and the patient was discharged after six days.

Case 40. Patient presented with a history of chilliness, feverishness, lassitude, headache, anorexia, nausea, vomiting, abdominal discomfort, dark urine, and a fine, generalized rash for four days. Examination on the eighth day of illness revealed no palpable liver, but marked tenderness to palpation in the right upper quadrant, and palmar erythema. Urine bilirubin on the seventh day of illness was 4 plus, and on the twenty-second day after onset was negative. Patient was discharged after 27 days' hospitalization.

Case 45. Patient presented with a history of loss of appetite, nausea, vomiting, backache and dark urine for three days. Examination on the fifth day of illness revealed a nontender liver 6 cm. below the costal margin, no splenomegaly, and several spider angiomata. Urine bilirubin on the third day of illness was 2 plus. Patient was discharged after nine days.

Of the physical signs, the occurrence of typical spider angiomata in 14 patients particularly impressed the investigators. These usually appeared during the first week after the onset of icterus, and disappeared during convalescence. Palmar erythema was noted in nine cases. These signs were seen in the more severely ill patients, and a definite relationship between these signs and severity was felt to exist.

A test for urine bilirubin was carried out in 42 cases early in the course of these illnesses and was confirmatory in all instances. Liver function

studies were carried out by the Communicable Disease Center laboratories in 13 unselected cases. The results of these tests are presented in table 3. Laboratory confirmation of hepatocellular disease was obtained in all instances.

The length of hospitalization for cases ranged from six to 70 days, with an average of 24 days. Although no relapses were observed in cases after medical discharge from the hospital ward, four cases relapsed during the course of their convalescence. Further bed-rest was adequate to permit recovery in these patients.

TABLE 3

Laboratory Data on Blood from 13 Hospitalized Cases

Case Number	Bilirubin Total mg.%	Thy. Turb. Units	$ZnSO_4$ Turb. Units	Ceph. Floc.
24	6.48	14.9	8.6	3+
25	4.00	4.3	6.9	3+
26	9.16	7.7	7.6	1+
27	1.26	23.3	13.2	3+
28	1.76	15.3	7.4	3+
29	1.00	2.3	6.5	3+
30	4.10	5.9	3.1	3+
31	1.96	4.4	4.5	2+
32	2.38	11.3	10.4	3+
33	4.0	10.8	—	—
34	6.96	17.0	11.7	4+
35	3.26	12.2	13.5	3+
36	0.66	17.2	11.8	3+

Normal Values: Bilirubin, 1.5 mg.%
Thy. Turb., 0 to 5 units
$ZnSO_4$ Turb., 0 to 6 units
Ceph. floc., 0 to 2+

Cases 9 and 38 developed progressive jaundice, ascites and neurologic signs, and died 15 and 30 days, respectively, after the onset of their illness. A liver biopsy performed on case 9 prior to death revealed the pathologic characteristics of fulminant hepatitis.

Although the clinical syndrome was characteristic of viral hepatitis, 12 acute and convalescent sera obtained from hospitalized patients were tested for the presence of heterophil antibodies and antibodies to leptospira and brucella. These studies yielded negative results.

POPULATION DATA

Statistics concerning the prison population were not kept other than for immediate administrative purposes. The only data available were total prison population on December 31, and June 30, beginning with the year 1950, and a census by race and by quarters occupied which was posted daily but not recorded.

The rapid change in inmates comprising the population due to entries and releases made necessary some attempt to obtain accurate data to deter-

mine rates. As of October 19, 1955, a census was made which included name, age and date of entry, and this information was coded and key-punched for tabulation. Weekly lists of entries and discharges were kept for a three-month period with the same information for each inmate, and these data were also key-punched. From this, stability of the population with regard to racial and age composition and weekly fluctuation in census was determined.

Epidemiologic Data

Morbidity Rate: The 45 cases in a population of 2,377 would represent a rate of 18.9 per 1,000 for the 11-month period. This and subsequent rates are not true rates, since they do not account for the population change

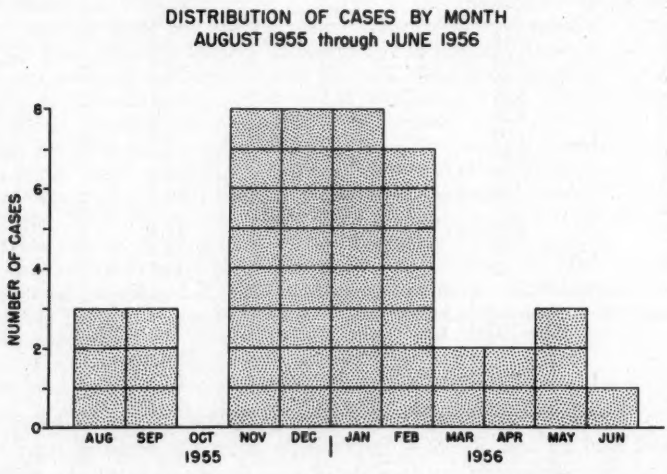

Fig. 1.

which was occurring continuously, as discussed above; however, this figure does provide a partial index of the risk of the disease in the institution.

Distribution of Cases in Time: Figure 1 indicates the distribution of cases by date of onset during the 11-month period of observation. A definite rise and fall in the incidence of the disease during this time may be seen. Thirty-one of the 45 cases occurred during the four months, November, 1955, through February, 1956.

Distribution of Cases by Race: There were 42 cases in whites and three cases in Negroes during the period of study, representing rates of 21.9 and 5.9 per 1,000, respectively.

Age Distribution: Table 4 gives the distribution of cases and attack rates for the age groups in the institution. Attack rates are high among men aged 16 through 34, with a decrease in rate among men 35 and older.

TABLE 4
Age Distribution, Cases of Viral Hepatitis

Age Group	Cases	Population*	Rate per 100
16–19	5	98	5.1
20–24	11	465	2.4
25–29	10	553	1.8
30–34	12	408	2.9
35–39	2	245	0.8
40–44	3	229	1.3
45–49	0	134	0.0
50 and over	1	245	0.4

* Based on census figures for October 19, 1955.

Dormitory Distribution: Table 5 indicates the quarters occupied by cases prior to onset. Because of the frequency of change of quarters within the institution, the distribution has been considered in relation to the incubation period of both types of viral hepatitis, and the table indicates the quarters occupied: (1) two to six weeks prior to onset, that is, within the range of the incubation period of infectious hepatitis; and (2) six to 24 weeks prior to onset, within the range of the incubation period of serum hepatitis. One case had his onset six weeks after entry, and therefore does not appear in the second group. The difference in the distribution of cases during the two periods is a reflection of the frequency with which changes in quarters were made. Twenty-six cases had occupied the same quarters during all of the six months prior to onset, 14 had occupied two different quarters, and five had occupied three.

It may be seen that over half of the cases came from dormitories 1, 2 and 3, which housed only 20% of the inmate population.

Lapse of Time from Entry to Onset of Illness: The length of time from

TABLE 5
Quarters Occupied Prior to Onset, Cases of Viral Hepatitis

Quarters	Census*	2 to 6 Weeks Prior to Onset	6 to 24 Weeks Prior to Onset
Dormitory 1	268	18	11
2	113	5	6
3	263	8	11
4	200	1	2
5	222	2	2
6	259	2	2
7	70	0	0
8	117	1	1
9	299	3	5
Quarantine	72	0	1
Tuberculosis ward	11	1	1
Cell block	21	2	1
Outside institution	462	0	0
Total	2377	44	43

* Based on census figures for October 19, 1955.

entry to onset ranged from 47 days to over seven years, with a median of 14 months and a mean of 17.0 months.

Transmission

Person-to-Person Spread: In a closed institution, ample opportunity for person-to-person spread, either directly or through fomites, is afforded, especially in one such as this, in which most of the inmate population had opportunity to have contact by visiting, and in which men were quartered very close together in the dormitories. There are several observations which are not entirely consistent with person-to-person spread, as in explanation: (1) Case 2 had been in the tuberculosis ward for four months prior to onset. The only contact with others not also confined to the ward was with the inmate nurses. (2) Cases 9 and 38 were in isolation cells at the time of onset, and had been there for three and two months, respectively. (3) During this period there were approximately 200 prison employees, most of whom had as close contact with the inmates as can be postulated to have occurred between most inmates not occupying the same dormitory. No cases occurred in this group. (4) There were 27 inmates who served on the hospital staff during this period and who had very close contact with the cases. None of this group became ill, despite the fact that none was protected by immune globulin. For these reasons, it is felt that person-to-person contact is not an adequate explanation.

Common Source Spread: Food for all inmates at the institution and for prison employees is prepared at the same time in a central kitchen. Milk is obtained from herds on the prison farm by automatic milking machines and is immediately pasteurized and placed in bulk containers. The water supply serves the entire institution, including the administrative offices, and is consumed by both inmates and employees. No cases of hepatitis were known among food handlers or those working at the prison dairy. As noted above, no cases occurred among employees. Most important, the pattern of the disease within the institution was in no way consistent with a common source spread. The occasional transmission of the infection through sharing items of food sent from outside the institution cannot be excluded.

Spread by Parenteral Injection: It was found that a number of opportunities for parenteral transmission by contaminated instruments existed.

1. *Routine Injections:* All inmates, on entry, were routinely given typhoid vaccine intramuscularly and smallpox vaccination. These were given on a mass basis by inmate nurses, and for the typhoid vaccination the same syringe and needle were used for all injections, the needle being wiped with alcohol between injections. This was also a common practice in the hospital for giving streptomycin to tuberculous patients, and penicillin or parenteral vitamin preparations to those requiring them. When carried out, however, sterilization was by means of autoclave at 15 pounds pressure for 30 minutes.

2. *Dental Procedure:* Dental care was given by an inmate who had formerly been a dental technician. Sterilizing of instruments was by boiling and was probably not practiced or was inadequate on many occasions, although documentation of this was not possible.

3. *Tattooing:* It was found that tattooing was a common practice among white inmates using improvised tools such as straight pins, sewing needles and writing pens. Tattooing was often carried out in small groups using the same instrument or an instrument borrowed from someone else.

4. *Illicit Use of Drugs:* Information obtained from inmates indicates that amphetamine tablets and barbiturate capsules were sold illicitly within the institution. Inmates who used these drugs intravenously took the medication to the owner of a syringe and needle, who would inject the drug for

TABLE 6

Exposure to Possible Parenteral Transmission, Cases of Viral Hepatitis

	No. of Cases	Per Cent
Routine immunization within 6 months	8	18
Injection at prison hospital within 6 months	14	30
Dental procedures within 6 months	18	40
Tattoo within 6 months	8	18
Use of intravenous drugs		
Implicated *	35	78
Admitted	6	13
Signs of use of intravenous drugs		
Definite	21	47
Doubtful	6	13

* Includes six admitting use who were implicated by others as well.

a fee as a reimbursement for the risk assumed. The practice was to crush and emulsify the drug in tap water prior to injection. Between injections, the syringe and needle occasionally were rinsed in boiling water, but no other sterilization was practiced.

Table 6 gives the findings in the 45 cases with regard to history of exposure to one of the above means of parenteral injections, and also physical signs of intravenous drug use. Inflammation about a puncture mark over or near a vein, or scarring over or about a vein on the hands or forearm, often associated with bluish discoloration of veins, was considered as a sign of the use of intravenous drugs in the absence of a history of receiving injections at the prison hospital.

Once the inmates were confident that the information given to the investigators would not be divulged, six cases admitted the use of intravenous drugs within the six months prior to onset and were willing to name others who shared this practice. An additional 29 of the cases were implicated in this way, or by three other inmates also willing to give information.

Of the 10 cases not so implicated, five had definite signs of needle use, and two had doubtful signs. Three had had injections at the prison hospital, four had had dental procedures, and one a tattoo in the preceding six

months. Of three with no history of any of the above, two had definite signs of needle use.

Since dormitories 1, 2 and 3 appeared to be the focus of drug use and contributed over half of the cases, an effort was made to obtain information related to the use of drugs intravenously in these dormitories. A complete dormitory listing was obtained and was reviewed with five inmates who were willing to name those known as users of drugs. The list was reviewed with each of these inmates independently and the information combined to obtain a list of those known to use drugs. The reliability of these data is open to question and subject to the bias that those developing hepatitis after

TABLE 7

Hepatitis by Dormitory Among Needle Users and Non-Needle Users

Dormitory Number	Number Inmates*	Number Cases†	Rate/100
1			
Needle user	32	9	28.1
Non-needle user	202	5	2.4
Total	234	14	
2			
Needle user	19	6	32
Non-needle user	96	0	0.0
Total	115	6	
3			
Needle user	44	7	16
Non-needle user	183	0	0.0
Total	227	7	
Total			
Needle user	95	22	23
Non-needle user	481	5	1.0
Total	576	27	4.7

* Based on dormitory census, February 27, 1956.
† Cases, November 1, 1955, to May 31, 1956.

drug use would probably have been talked about in association with this fact; however, it is felt that the data have some validity when these limitations are kept in mind. Table 7 presents the data concerning the rate of hepatitis among those inmates in dormitories 1, 2 and 3 who were known to use drugs and those not implicated. It may be seen that there is a definite association of hepatitis with drug use, and the difference is statistically significant (Chi-square equals 86.87; p less than .001).

The investigators were frequently informed that inmates developing jaundice were reluctant to present themselves at the hospital for treatment of their illness because of apparent recognition of an association between the use of drugs intravenously and the occurrence of jaundice. For this

TABLE 8

Survey, Dormitories One and Nine

	Dormitory 1		Dormitory 9	
	Number	Percentage	Number	Percentage
Total seen	93		97	
History of jaundice in the past	6	6.4	6	6.1
Recent illness				
Compatible with mild hepatitis	5	5.3	2	2.0
Upper respiratory infections	14	15.0	8	8.2
Other, acute and chronic	5	5.3	9	9.2
Signs				
Jaundice	0	0.0	0	0.0
Enlarged and palpable liver	7	7.5	6	6.1
Hepatic tenderness	7	7.5	4	4.1
Palpable spleen	0	0.0	0	0.0
Spider angiomata	5	5.3	0	0.0
Needle marks				
Definite	15	16.1	7	7.2
Doubtful	10	10.7	10	10.3
Urine bilirubin				
1 plus	4	4.3	2	2.0
Trace	2	2.1	0	0.0

reason, a survey was carried out. Dormitories 1 and 9 are similar in physical facilities and in the number of inmates housed. Dormitory 1, however, contributed a much larger number of cases, and this dormitory was named as the one in which those using intravenous drugs tended to group. Dormitory 9, on the other hand, was said to have few drug users. From the dormitory list, every third name was taken and these inmates were examined. A brief history was obtained and each man was examined with regard to jaundice, hepatomegaly, hepatic tenderness, splenomegaly, spider angiomata and needle marks. Urine was tested for bilirubin. The results of this survey are indicated in table 8. No inmates with jaundice were found, but a small percentage from each dormitory had physical findings. The number of inmates from dormitory 1 evidencing definite signs of drug use was twice

TABLE 9

Correlation, Physical Findings and Needle Scars

Dormitory 1	Total	Enlarged Liver		Tender Liver		Positive Urine Bilirubin		One or More Findings	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Needle scars	15	6	40	3	20	2	20	7	47
No needle scars *	78	1	1.3	4	5.1	2	3.8	7	9.0
Dormitory 9									
Needle scars	7	0	0	1	14	1	14	1	14
No needle scars *	90	6	6.6	3	3.3	1	1.1	7	7.8

* Includes those with skin markings classified as doubtful needle scars.

that in dormitory 9. Table 9 shows the correlation of positive physical findings with needle marks. A striking relationship exists in the inmates from dormitory 1 which is not seen in those from dormitory 9.

The evidence obtained is felt to indicate that the opportunity for parenteral transmission of viral hepatitis existed, and that the associations found strongly suggest that this was the responsible mode in many of the inmates.

Etiology

The route of infection is an important factor in differentiating infectious from serum hepatitis. Where person-to-person spread or ingestion of infectious material can be demonstrated, it may be assumed that the agent is that of infectious hepatitis, since volunteer studies have failed to demonstrate infection with the agent of serum hepatitis except by parenteral inoculation. When parenteral inoculation is suspected, serum and infectious hepatitis must be considered, since both agents can be transmitted in this way. Parenteral transmission probably occurred in this instance; therefore, other differential features will be considered.

Incubation Period: Incubation period is the most reliable means of distinguishing infectious from serum hepatitis epidemiologically. The incubation period of infectious hepatitis is not usually over 45 days, and that of serum hepatitis not usually under 60 days.

Cases 6 and 10 had their onset 62 and 47 days, respectively, after entry. Neither gave a history of exposure to a known case of hepatitis. Case 10 received routine injections and had two teeth extracted within several days after entry. He was implicated in drug use, but no earliest date could be learned. Case 6 received routine immunizations and admitted drug use, but refused to give any date for such use. If the infection occurred within the institution, the incubation period in these two instances would suggest infectious hepatitis but is within the limits of the range of 31 to 151 and 34 to 213 days observed in clinic and hospital patients developing hepatitis following injections.[2, 3]

As noted above, cases 9 and 38 were in isolation cells at the time of onset and had been in isolation for three and two months, respectively. Case 38 admitted drug use, and this was the violation which resulted in his confinement to the cell block. Case 9 was implicated, and needle marks were found on examination. Drugs probably were not obtained in the cell block, so that the incubation period accords with that of serum hepatitis.

No exclusive dates can be fixed for other cases; however, one other observation may be considered in this respect. It was learned that during August and September only one syringe and needle were available, due to confiscations of other sets by authorities. Prior to this there had been two to four sets in use in the prison yard at any one time, with a separate set in the Negro dormitories. During August and September the one set allegedly was used by all inmates taking drugs. As can be seen from figure 1, most

cases occurred from November through February, three to six months after this.

An administrative change in January resulted in much stricter discipline, with curbing of many practices previously carried on. The decline in incidence began two months later.

Value of Immune Globulin: Immune globulin has been demonstrated to be of definite prophylactic value in infectious hepatitis but not in serum hepatitis.[4] An attempt was made to use this difference to document which type was present in the institution. On February 29 and March 1, immune globulin in a dose of 2 ml. was given to half of the inmates selected at random in dormitories 1, 2 and 3. During the four months following, five cases of hepatitis occurred in men from these dormitories. Table 10 summarizes the epidemiologic findings.

TABLE 10

Epidemiologic Data, Cases Following Administration of Immune Globulin

Case Number	Immune Globulin	Interval Until Onset	Needle Marks
39	Yes	21 days	Definite
41	No	—	Definite
42	No	—	Definite
44	Yes	56 days	Questionable
45	No	—	Definite

It is to be noted that four of the five cases showed needle scars on physical examination, while the remaining case had marks on his skin classified as doubtful needle scars. The two cases who received immune globulin are too few to permit definite epidemiologic identification of the agent involved. The occurrence of hepatitis in these cases, coupled with the data on incubation period, is felt to be highly suggestive that the serum hepatitis virus was operative in this institution. The decline in incidence following the use of immune globulin is felt to be due to other factors.

Possible Source of Serum Hepatitis: It has been estimated that 0.35 to 0.5% of blood donors are carriers of the virus of serum hepatitis.[5, 6] It is not difficult, therefore, to postulate its introduction by a carrier in these circumstances. In addition, an inmate who was inoculated experimentally at another prison with known icterogenic material without having developed clinical or laboratory signs entered the institution in November, 1953, and was implicated in drug use. It is possible he may have been an asymptomatic carrier and introduced this type into the institution.

DISCUSSION

There is adequate evidence that viral hepatitis may follow intramuscular injection,[3, 7] dental procedures,[8] tattooing,[9, 10] and use of narcotics by parenteral routes.[11, 12] While both infectious and serum hepatitis may be transmitted by parenteral inoculation, in instances where jaundice has been ob-

served after exposure to one of the means mentioned the incubation period has usually been that of serum[2, 8, 9, 10, 13, 14] rather than infectious hepatitis.[7]

It is felt that the evidence in the present instance is adequate to indicate the probability of transmission by the parenteral route, and of the agent's being that of serum hepatitis. Perhaps the strongest evidence is the fact that the association of drug use and hepatitis was made by the inmates themselves, and it was they who suggested this possibility to the investigators before the latter became aware of the practices within the institution.

Within a seven-month period, 22 cases occurred from three dormitories in 95 inmates known to be using drugs. This is an attack rate of 23%, and accords well with previous observations of persons exposed in diabetic and venereal disease clinics.[13, 14] In addition, there was a significant association of hepatomegaly, hepatic tenderness and bilirubinuria in the inmates surveyed. Forty-seven per cent of the men from dormitory 1 with definite evidence of needle scars had one or more positive physical or laboratory findings, whereas of those with no evidence of needle use only 9% had one or more findings. None in either group was symptomatic.

The occurrence of long-term asymptomatic carriers of the serum hepatitis virus is well documented.[15] The risk of high carrier rates is likely to increase in closed populations where illicit drug use and narcotic addiction are prevalent. This has implications not only within the group studied but also as a general health problem, since they may act as blood donors.

When prisons are used as blood donor sources, a careful investigation for occurrence of hepatitis in the institution should be carried out. In addition, all donors should be rigidly screened for evidence of needle marks and such persons rejected. Even this, however, will not exclude all danger from narcotic users. The brachial, saphenous and femoral vessels may be used to avoid detection, as the skin over these is not usually examined. In addition, signs may not occur. In the absence of a reliable diagnostic method to detect infectious carriers of the virus, it would seem better to exclude as donors closed population groups in which jaundice is prevalent.

Summary

The clinical and epidemiologic observations concerning 45 cases of viral hepatitis are presented. These cases were studied in a penal institution over an 11-month period. The epidemiologic data obtained indicate that parenteral transmission of the serum hepatitis virus via contaminated syringes and needles caused the outbreak. The implication of these findings as related to blood collection programs in a closed population group is discussed.

Summario in Interlingua

In un institution penitentiari in que hepatitis virusal habeva devenite prevalente durante le previe duo annos, un studio del comportamento epidemiologic del morbo esseva effectuate. Esseva observate 45 casos—39 icteric, sex anicteric—durante un

periodo de 11 menses. Le datos clinic e laboratorial esseva de accordo con le diagnose. Confirmation pathologic esseva obtenite in un del casos. Duo casos se terminava in exito mortal.

Esseva constatate que 42 del 45 patientes habeva recipite in le curso del precedente sex menses immunisation routinari, injection de un medication, labor de dentista, tatuage, o administration illicite de drogas. Vinti-un habeva definite signos de acupunctura, incluse duo del tres sin historia de intervention de ulle del supra-listate typos. Es opinate, per consequente, que inoculation parenteral accidental esseva le methodo le plus significative de transmission.

Intra un periodo de septe menses, 22 casos del morbo occurreva in un gruppo de 95 residentes de tres dormitorios in que drogas esseva cognoscitemente in uso. In plus, le investigation de duo dormitorios revelava un correlation positive de hepatomegalia, sensibilitate hepatic, e bilirubinemia con signos physic de acupunctura. Isto justifica le conjectura que le infection esseva plus general que lo que esseva evidente ab le numero del casos.

Le datos epidemiologic suggere que le hepatitis in iste institution esseva predominantemente del typo seral plus tosto que del typo infectiose. Iste observationes debe esser prendite in consideration quando residentes de institutiones penitentiari es usate como donatores de sanguine.

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DIET, BLOOD LIPIDS AND HEALTH OF ITALIAN MEN IN BOSTON *

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INTRODUCTION

THE hypothesis that ingestion of excess dietary fat leads to coronary arterial and heart disease is man is supported by much suggestive evidence but has yet to be demonstrated by rigorous proof. Atherosclerosis, including coronary atherosclerosis, has been induced in a variety of animals by different experimental regimens. Generally these involved the feeding of cholesterol and a high intake of fat. Under certain conditions the latter causes hypercholesterolemia and hyperlipoproteinemia in man, but firm evidence is lacking that coronary heart disease in man is caused by either overnutrition of fat or by over- or undernutrition of any other nutrient.[1]

Epidemiologic studies may be expected to indicate etiologic relationships in disease even when knowledge of pathogenesis remains imperfect. The behavior of disease in communities is no less valid a field for research than is the behavior of disease in patients or in body tissues or cells; rather, epidemiologic investigation complements the other two basic methods of studying disease.[2] In recent years such epidemiologic investigations have become more common in cardiovascular disease, and many have been widely reported to support the hyperlipophagia-hyperlipemia hypothesis of causation in coronary heart disease.[3]

Among his pioneering activities in this field, Keys and co-workers have reported [4, 5] that Neapolitan laborers, whose diet contains only about 20% of calories from fat, enjoy significantly lower serum cholesterol levels and apparently less frequent heart disease than do similar groups of workers in the United States, where the consumption of fat is around 40% of the caloric intake. That this effect is due more to diet than to "race" is supported by the finding that the more affluent Neapolitan professional men and the Bolognese workers, whose diets are richer in fat, have correspondingly higher blood cholesterol concentrations and seem more commonly to suffer from coronary heart disease than do the Neapolitan workers.

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To determine further whether environmental or constitutional factors are the more important in relation to the low blood lipid levels observed in these Neapolitans, and to evaluate carefully the dietary habits and cardiovascular status of a comparable group of men living in the environment of the United States, the observations to be presented in this report were made on a group of first-generation Neapolitan-Americans in Boston.

Experimental

The problem of locating and studying a sufficiently large sample of adult male workers whose parents had been born in the environs of Naples but who themselves have lived all or nearly all of their lives in the United States was met by the coöperation of the B. F. Goodrich, Footwear and Flooring Co., a large industrial firm which employs a great number of men of Italian ancestry living in the Boston area, and which generously agreed to permit our research team to carry out the necessary examinations within the factory during working hours. Of the nearly 300 men who fulfilled the criteria of age (between 20 and 50 years) and of Neapolitan parentage but American residency, 213 agreed to be subjects and were examined. In what ways those who did *not* volunteer may have differed in regard to health and other characteristics from those who did and who are here reported is not known, nor can it be presumed that these subjects are representative of all first-generation Neapolitan men who reside in the Boston area. Such uncertainties are inherent in all volunteer groups, but it was neither feasible nor desirable to force the attentions of the study upon a randomly selected sample. The enthusiastic interest and wholehearted coöperation of the volunteer workers, the management, and of Dr. Louis R. Daniels, the medical director of the employing company, are gratefully acknowledged.

The entire examination required about one hour and a half per man. This included a 45 minute diet interview,* and a modified Burke diet history.[6] In addition to the diet interview, a questionnaire was sent to the subject's wife. This questionnaire provided information as to the cooking methods, purchase of fats and oils, and types and amounts of meats, poultry and fish, cheese, and other fat-contributing foods. A food table compiled from various sources was used for the dietary calculations.[7] The principal sources for the food table were Handbook No. 8,[8] Okey,[9] Pihl[10] and Hilditch.[11] The diets were estimated for calories, animal and vegetable protein, animal and vegetable fat, saturated and unsaturated fatty acids, the "essential" fatty acids (linolenic, linoleic and arachidonic), plus the more usual minerals and vitamins.

A necessarily brief but adequate medical history and physical examination by an internist established the presence or absence of manifest coronary

* Miss Olive Hayes and Miss Gertrude Rose, of the Department of Nutrition of the Harvard School of Public Health, aided in the interviews and the subsequent analyses of the diets.

or other cardiovascular disease.* Physical activity patterns and anthropometric data, including bi-acromial and bicristal diameters, and skinfold thicknesses over the triceps and subscapular region, measured by a type caliper suggested by Keys and Brozek, were recorded. A blood sample for total serum cholesterol and Sf_{12-20} and Sf_{20-100} lipoprotein determinations, urine for sugar and albumin, and a 12-lead electrocardiogram were taken on each man.

No subject with overt cardiovascular disease was included in the analysis, in conformity with the practice of Keys in Naples. To obtain the group of healthy subjects which he reported, Keys, in a personal communication, states that in the entire material of about 1,000 men studied in the years 1952 to 1955 in Naples and Sardinia, fewer than 25 men were excluded and only six or seven were cardiovascular, half of the latter being found among the small group of "bankers" in Naples. In our original study

TABLE 1

Mean Blood Lipid Concentrations, mg. per 100 ml. Serum, with Age

Age	Number	Total Cholesterol		Sf_{12-20}		Sf_{20-100}	
		Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
20–29	38	227.9	40.0	26.7	13.6	59.9	37.5
30–39	73	236.9	39.0	33.8	16.7	83.2	73.0
40–50	78	246.9	45.0	37.9	21.1	89.3	76.0
All ages	189	239.2	42.4	34.6	18.30	83.0	69.00

group, one man had possible angina pectoris; another had rheumatic heart disease; another auricular fibrillation, cause undetermined; two had intermittent claudication, and one suffered from severe hepatic cirrhosis from which he later died. These men were excluded, as were two men with unilateral leg amputation, because of inability to determine their true body weight, another because of inability to obtain a satisfactory blood specimen, and 15 more because they had come to America after 10 years of age, which had been placed as the arbitrary deadline for their beginning residence in this country.

RESULTS

One hundred eighty-nine subjects remained who fulfilled all criteria for the study; the data from this group are presented in the following analyses.† The age distribution by decades in relation to mean blood lipid concentrations for each age group is presented in table 1. About 20% of the men fall into the 20 to 29 age range, with about 40% in each of the next two

* Dr. John Scharffenberg and Dr. Leonardo Sinisterra aided in the clinical evaluations,
† Mr. Sidney Abraham, statistician with the Heart Disease Control Program, U. S. Public Health Service, helped immeasurably with the statistical analyses.

decades. Because of the difference in lipid levels between these groups it is important, in analyzing other measurements, to take the age factor into account.

The rise in serum cholesterol with age is in agreement with the findings of Keys and others [3] who have studied groups of normal men in this country.

TABLE 2

Mean Total Cholesterol Concentration, mg. per 100 ml. Serum, with Age, in Men Studied in Naples* and Boston

Boston						Naples					
No.	Age in Years			Cholesterol		No.	Age in Years			Cholesterol†	
	Range	Mean	Std. Dev.	Mean	Std. Dev.		Range	Mean	Std. Dev.	Mean	Std. Dev.
71	20–34	29.1	3.5	227.7	31.7	40	20–34	27.9		175.4	32.4
118	35–50	42.1	3.8	246.6	43.5	43	35–54	42.6		193.4	31.9
189	20–50	37.2	7.3	239.2	42.4	83	20–54	35.5	8.9	184.7	33.2

* Data from Arch. Int. Med. 93: 331, 1954.
† Cholesterol values were corrected by a factor of 0.836 to account for difference is cholesterol method then used, according to Clin. Chem. 1: 34, 1955.

As shown in table 2, the cholesterol levels of the Naples group are significantly lower in both age groups than are those of the Bostonians, an indication that the relatively low level of the Neapolitans is due not so much to the host as to environmental factors.

TABLE 3

Mean Total Cholesterol Concentrations, mg. per 100 ml. Serum, with Age and Relative Weight

Age	Relative Weight							
	Under 100		100 to 119		120 and more		Total	
	No.	Chol.	No.	Chol.	No.	Chol.	No.	Chol.
20–29	8	197	24	242	6	208	38	228
30–39	14	236	34	237	25	234	73	237
40–59	25	235	37	251	16	253	78	247
All ages	47	223	95	243	47	232	189	239

The effect of body weight upon blood lipid levels is seen in table 3 to be considerable, and is independent of age. (The older age group is somewhat under-represented in the overweight group, and over-represented in the underweight group.) Relative weight values expressed as per cent of "standard" weight were calculated from the tables of standard weights for age, sex and height resulting from the Medico-Actuarial Investigation of

1912,[12] distributed by the Metropolitan Life Insurance Company. It should be remembered that this standard weight allows for a moderate gain with age; no attempt was made to relate observed weight to "ideal" or "desirable" weight which remains constant with age. It is of interest that the mean cholesterol level of the grossly overweight group is lower than that of

TABLE 4

Mean Total Cholesterol Concentrations, mg. per 100 ml. Serum, with Skinfold Thicknesses, Sum of Triceps and Subscapular in cm.

Age	Skinfold Thickness							
	1.0–2.4 cm.		2.5–3.9 cm.		4.0 cm. & over		Total	
	No.	Chol.	No.	Chol.	No.	Chol.	No.	Chol.
20–29	14	228.6	22	238.6	2	217.0	38	227.9
30–39	22	238.6	29	238.8	22	236.4	73	236.9
40–50	30	235.6	29	247.4	19	251.3	78	246.9
All ages	66	234.1	80	240.0	43	242.4	189	239.2

the moderately overweight group, suggesting that obesity per se does not strongly affect blood lipid levels.

Since total body weight is comprised, in different individuals, of different proportions of fat, muscle and bone, it is evident that relative weight values, except in extreme ranges of overweight or underweight, do not necessarily indicate true obesity or leanness. The thickness of subcutaneous fat from

TABLE 5

Relative Weight with Skinfold Thicknesses

Skinfolds	Less Than 90%	90–109.9%	110–119.9%	Over 120%	Total Number
	Number	Number	Number	Number	
1.0–1.9 cm.	14	29	0	0	43
2.0–2.4 cm.	2	13	7	2	24
2.5–3.9 cm.	1	30	30	18	79
4.0–4.4 cm.	0	5	5	11	21
4.5 cm. and over	0	2	4	16	22
	17	79	46	47	189

certain regions of the body, as quantitated by standard skinfold calipers, is considered by some workers to reflect total body fat fairly accurately.[18] To determine whether this measure of obesity may be more or less strongly related to elevated blood lipids than is relative weight, the sum of the triceps and subscapular skinfold thicknesses was related to serum cholesterol values in the analysis summarized in table 4. Mean total serum cholesterol concentration of the moderately obese group is somewhat increased over that

of the thin group, but that of the grossly obese group does not show a corresponding increase, again suggesting that excess fatness is not strongly related to elevated blood lipids. The distribution of "overweight" and "obesity" does not, however, appear to be too divergent in this group of men. As seen in table 5, no one with skinfolds of less than 2 cm. is in the 110% or greater relative weight category, and no one with skinfolds greater than 4 cm. is in the less than 90% category. Tables 6 and 7 give comparative figures for both relative weight and skinfold thicknesses of the Naples and Boston groups, showing the Bostonians to be heavier by both measurements. Within each category of skinfold thickness, however, the serum cholesterol of the Boston group is significantly greater, suggesting again that something other than increased body fat is responsible for their higher lipid levels.

TABLE 6

Percentage Distribution of Relative Body Weight of Men Studied in Naples and Boston

	Relative Weight							
	Less Than 80%	80–89%	90–99%	100–109%	110–119%	120–129%	130% and Over	Total
Naples	5.0	17.1	27.5	25.7	15.3	6.3	3.1	100.0%
Boston	1.6	7.4	15.9	25.9	24.3	17.5	7.4	100.0%

TABLE 7

Mean Cholesterol Concentrations with Skinfold Thicknesses of Men Studied in Naples and Boston

	Skinfold Thicknesses (Triceps plus Subscapular, in mm.)			
	8–23 mm.		23–83 mm.	
	Number	Cholesterol	Number	Cholesterol
Naples	64	151.7	64	180.8
Boston	54	229.6	135	239.7

Mesomorphic body build has been thought to confer a higher risk of coronary disease than does that of ecto- or endomorphic build.[14] Our estimates of somatotype did not prove amenable to analysis, but the two measurements of lateral build—bicristal and bi-acromial diameter—were used as indicators of "mesomorphy" or "laterality" to determine whether blood lipids of the mesomorph might be at a higher level.

Using the formula $\frac{\text{bi-acromial} + \text{bicristal}}{\text{height}}$ as a measure of relative laterality, we found as shown in table 8, that the broadest group actually had the lowest mean cholesterol level.

Because "masculinity" has been considered by some [15] to predispose to coronary heart disease, the formula $\frac{\text{bi-acromial}}{\text{bicristal}}$ was taken as a measure of maleness and related to blood cholesterol concentrations (table 9), again with not a positive but rather a slight negative correlation, statistically not significant.

TABLE 8

Mean Total Cholesterol, with Relative "Laterality" and Age

Age	Relative Laterality				Bi-acromial plus Bicristal Diam. / Height	
	Narrow (less than .38)		Medium (.39–.40)		Broad (.41 and over)	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	12	234	20	222	6	231
30–39	14	233	38	241	21	229
40–50	13	244	43	252	32	236
All ages	39	237	101	242	49	233

One of the main purposes of this study was to measure dietary intake, especially of fats, in order to compare consumption of total fat of the Boston with the Naples group. It was further planned to compare subgroups within the Boston population, segregated according to levels of intake of various fats and other nutrients, to test for their possible relationship to blood lipid levels.

TABLE 9

Mean Total Cholesterol, with Relative "Masculinity" and Age

Age	Relative Masculinity				Bi-acromial Diameter / Bicristal Diameter	
	Least (1.15–1.29)		Medium (1.30–1.39)		Most (1.40 and over)	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	10	226	17	230	11	225
30–39	24	232	35	241	14	239
40–50	29	257	39	238	10	248
All ages	63	243	91	237	35	234

The dietary intake of the Italians from the Keys study and the Italian-Americans is shown in table 10. In both instances the assessed intakes are greater than the national averages. The fat intake of the American group is approximately two and one-half times greater than that of the Italian firemen, with twice the percentage of calories coming from fat. Italian-Americans also consumed higher protein diets, and thus the calories coming

from carbohydrates are appreciably lower in the American group. In table 11 a complete breakdown of the Italian-American diets is given. The intake of nutrients follows the pattern of other Americans, though the menu patterns are different because of nationality preferences. The dietary intakes showed considerable range within the groups. Calories ranged from 1,800

TABLE 10

Comparative Food Consumption Data

	Italian National*	Neapolitan Firemen*	U. S. A.†	U. S. A. Italians
Calories	2340	3010	3220	3450
Protein—gm.	75	97	97	120
% Calories Protein	13	13	12	14
Fat—gm.	50	65	148	164
% Calories Fat	19	20	41	43

* Data taken from Arch. Int. Med. **13**: 328–336 (1954)

† Data compiled from Consumption of Food in the United States, 1909–1952, Agriculture Handbook 62. Sept. 1953. U. S. D. A.

to 6,000 per day. About 10 subjects had less than 30% of calories from fat, and eight took more than 50% of calories from fat. Animal protein in the Italian-American group was generally high. Meat, fish or fowl was used twice a day and in generous quantities. Cheese was practically a daily food. Milk as a beverage was not particularly popular, but generous

TABLE 11

Approximate Food Intake of Italian-Americans in Boston

	Age		
	20–29	30–39	40–50
Number	38	73	78
Calories	3600	3600	3250
% Calories from fat	43	41	40
% Calories E.F.A.*	5	5.1	5.0
% Fat E.F.A.*	12	12.9	12.7
% Fat—animal	77	74	71
% Calories protein	15	14	14
% Protein animal	75	73	72
% Calories alcohol	5	6.8	6.3
Mg. cholesterol	903	746	714

* E.F.A. = "Essential" fatty acid.

quantities were used in their very frequent cups of coffee. Some olive oil was used, but the other oils, such as cottonseed oil, or corn oil, or blends of the three oils, contributed more to the fat calories. Margarine as a spread or used in cooking was almost negligible. However, hydrogenated fats were often used in baked foods (cakes). Bacon fat was used frequently in the preparation of meat sauces.

Since caloric intake cannot be satisfactorily related to body weight without taking into account caloric expenditure, and since inadequate physical activity is thought [16] to predispose to elevated blood lipids and to coronary artery disease, each man was questioned in some detail about his usual physical activity both on and off the job, and the degree of his activity was compared with caloric intake and relative weight. Energy expenditure was graded on a three-point scale of less than usual activity, usual, and more than usual. Energy intake was expressed as percentage of basal caloric requirement, using the Boothby and Berkson nomogram,[17] which takes into account both surface area and age of each male individual. If these two parameters (energy intake and energy output) could be accurately measured, one would expect them to stand in fixed relationship to relative body weight, so that a thin, active man might well have a higher caloric intake than that of an obese, sedentary man of the same height. In table 12

TABLE 12

Caloric Intake, as Per Cent Above Basal Requirement, with Relative Body Weight and Physical Activity

Activity	Relative Weight								Total	
	Under 90%		90–109.9%		110–119.9%		Over 120%			
	No.	% Bas. Cal.	No.	% Bas. Cal.	No.	% Bas. Cal.	No.	% Bas. Cal.	No.	% Bas. Cal.
Low	3	114	28	105	19	105	14	89	64	103
Medium	11	114	39	111	15	111	19	82	84	105
High	3	153	12	122	12	103	14	69	41	99
	17	121	79	111	46	106	47	80	189	103

these data are set out, showing, as expected, an increase in caloric intake with increasing physical activity in the groups of normal and under 10% of normal relative weight. In the two overweight categories, however, this trend does not hold; in fact, the most overweight and most active men appear to ingest the lowest caloric intake relative to basal requirements. There is also a consistent trend in each activity category for relative caloric intake to *decrease* with increasing relative body weight, so that the most overweight in each activity category have the lowest intake.

This apparently paradoxic relationship is in part due to the method of calculating caloric intake as per cent of basal requirement, in which an overweight individual, with his greater surface area due to obesity, has a correspondingly *higher* basal requirement and thence a *lower relative* caloric intake than he would have if his weight were normal. Furthermore, the basal caloric requirement of obese individuals cannot be accurately calculated from the standard Du Bois tables, and the dietary patterns of the obese are notoriously difficult to determine.

The mean percentage of caloric intake in relation to basal metabolic requirement, as determined by the Boothby-Berkson chart, was 103% above basal. This may seem excessively high in light of the article of Epstein et al.[18] who used an activity allowance of 50% calories above basal for moderately active subjects, and 60% calories above basal for more rigorous workers. These investigators considered a dietary record suitable for inclusion in the study if it came within 130% of this figure. Even with this leeway, the top limit for dietary acceptance would be approximately 108% above basal requirement. The National Research Council[19] has recommended that the standard man of reference, age 25, receive 110% calories above the basal requirement, and the reference man, age 45, 80% above basal. In a study of Scottish miners and clerks,[20] the miners working hard for three and one-half hours of the eight-hour shift had an average intake of 147% above basal and the clerical workers 80%. These subjects varied in ages from 20 to 46. Energy expenditure was measured by the Kofranyi

TABLE 13

Mean Total Cholesterol, mg. per 100 ml. Serum, with Physical Activity and Age

Age	Physical Activity					
	Low		Medium		High	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	12	247.0	17	202.3	9	248.9
30–39	21	242.6	36	221.2	16	229.9
40–50	31	253.5	31	241.8	16	240.8
All ages	64	247.8	84	232.6	41	239.3

Michaelis respirometer, and all food was weighed by a dietitian. There was considerable range in percentage above basal in both the Scottish miners study and the Italian-American study. There are also difficulties in obtaining reasonably accurate dietary and activity data from all subjects. The subjects in this study attach a considerable importance to food, particularly to meat. The nutritionists, in their attempt to obtain detailed information concerning fat, may also overestimate. However, in the main the dietary histories seem to fit in between the office workers and the hard workers. It is also possible that some of these subjects may have been gaining weight or intentionally trying to lose weight, which would invalidate any per cent above basal caloric intake recommendation. We are satisfied that the diet histories in the main are realistic.

When one is relating physical activity to serum lipid concentrations it is important to take age into account, since older men might be expected to be less active than younger men and therefore to have higher lipid values by virtue of age per se, rather than because of decreased activity. There is

slight over-representation of the 40-to-50 year age group in the low activity category, but the age distribution is otherwise similar to that in the total sample (table 13). In each age group, blood cholesterol levels are higher in the least active than in the moderately active group, but in the most active they are again increased, although not to the level of the inactive group (except in the nine most active men of the 20-to-29 age range). These high lipid levels of the relatively sluggish men are not correlated with overweight since, as shown in table 14, the mean differences in weight are not appreciable, and in the 20-to-29 age group inactive men actually weigh less than the moderately active. Again, smallness of numbers in each subgroup, inaccuracy of activity estimates and errors in measurement of lipids [21] do not permit any definite conclusions.

TABLE 14
Relative Weight with Physical Activity and Age

Age	Physical Activity						Total	
	Low		Medium		High			
	No.	Rel. Wt.	No.	Rel. Wt.	No.	Rel. Wt.	No.	Rel. Wt.
20–29	12	106	17	111	9	107	38	108.3
30–39	21	115	36	109	16	119	73	112.8
40–50	31	108	31	105	16	108	78	106.6
All ages	64	112	84	108	41	112	189	109.6

When the possible effect of dietary fats upon blood lipid concentrations within this group was considered it was first divided into those who consumed more and those who consumed less than 40% of calories from fat. Although in the 20-to-29 age group the heavier fat eaters have higher serum lipids, this is not true in the older age groups, so that for all ages the group which consumed 40% or more of its calories from fat had slightly but not significantly lower mean values for total cholesterol, Sf_{12-20} and Sf_{20-100} lipoproteins than in the under 40% group (table 15). These findings do not necessarily conflict with those of Keys, who has found low blood lipid levels associated with low intake of dietary fat, since our figures are based upon small numbers of subjects, *all* of whom consumed relatively large amounts of fat. The mean per cent calories from fat of the "under 40%" group was 35%, which is much higher than the figure for native Neapolitans; the mean per cent calories from fat of the "over 40%" group was 45%. An examination of the ages of the two groups which are being compared shows that those consuming less than 40% of their calories from fat are somewhat older, with increased age thus responsible, in part, for their higher lipid levels. To account for age, an analysis of convariance was performed. Adjustment of both total groups for age changes the lipid

values only slightly, however, and application of the "f" test shows that the difference between the means, adjusted or unadjusted, is not significant.

It is of interest to note the relation between consumption of alcohol and consumption of fat in these men. Eight of the 10 men whose fat intake was less than 30% of total calories gained 15 to 24% of their calories from

TABLE 15

Mean Blood Lipid Concentrations, mg. per 100 ml. with Per Cent Calories from Fat and Age

Age	Per Cent Calories from Fat										Total	
	Under 40%					Over 40%						
	No.	%	Chol.	Sf_{12-20}	Sf_{20-100}	No.	%	Chol.	Sf_{12-20}	Sf_{20-100}	No.	%
20–29	7	10	221.6	17.9	35.7	31	27	228.7	29.2	65.4	38	20
30–39	28	38	237.7	32.9	96.8	45	39	235.0	33.9	74.7	73	39
40–50	38	52	248.9	40.0	96.6	40	34	243.7	36.8	83.4	78	41
All ages	73	100	242.6	36.1	82.9	116	100	237.1	33.6	76.3	189	100

alcohol, whereas the 12 subjects who consumed over 50% of their calories from fat used little or no alcohol.

When fat intake is categorized according to its animal or vegetable origin (table 16), no significant relationship is seen between the per cent fat of animal origin and blood lipid values. In this and other analyses, the Sf_{12-20} and Sf_{20-100} lipoproteins follow essentially the same distribution as

TABLE 16

Mean Blood Lipid Concentrations with Per Cent Animal Fat and Age

Age	Per Cent Animal Fat											
	50–69%				70–79%				80–99%			
	No.	Chol.	Sf_{12-20}	Sf_{20-100}	No.	Chol.	Sf_{12-20}	Sf_{20-100}	No.	Chol.	Sf_{12-20}	Sf_{20-100}
20–29	4	195.8	25.5	52.5	20	225.8	25.5	65.2	14	238.9	28.6	54.6
30–39	26	232.7	33.6	79.7	24	239.3	32.1	69.5	23	236.3	35.9	101.2
40–50	25	243.6	34.2	86.7	42	248.6	39.8	95.4	11	243.2	39.2	71.9
All ages	55	235.1	33.9	82.3	86	241.6	35.4	83.6	48	240.0	34.2	82.3

that for total serum cholesterol. Table 17 shows the coefficient of correlation values between these three serum lipids. In the analyses to follow, therefore, only the values for total cholesterol are used. The effect of fat upon serum cholesterol level has been shown to be less influenced by the animal or vegetable source of dietary fat than by the degree of saturation of the fatty acid moieties in the diet. The percentage of fats from unsaturated fatty acids and from the three "essential" fatty acids—linoleic,

TABLE 17

Coefficient of Correlation (r) Values for the Three Blood Lipid Measurements

	r
Total cholesterol with Sf_{12-20}	+0.46
Total cholesterol with Sf_{20-100}	+0.37
Sf_{12-20} with Sf_{20-100}	+0.60

linolenic and arachidonic—was computed for each subject, recognizing that such values are far from accurate due to errors of analytic technic in assessing dietary fat as well as in measuring fatty acid content of foods, and to variability of fatty acid content, both innate and acquired, in processing and cooking.

When unsaturated fatty acid intake is expressed as percentage of total calories, the mean blood cholesterol level is slightly lower in the group with

TABLE 18

Mean Total Cholesterol with Per Cent Calories from Unsaturated Fatty Acids and Age

Age	Per Cent Calories from "U.F.A."					
	Less than 22%		22–24.9%		25% and Over	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	11	225	14	232	13	225
30–39	26	239	29	230	18	241
40–50	32	248	27	256	19	230
All ages	69	241	70	240	50	232

the highest ingestion (table 18), but when it is expressed as percentage of total fat intake there is no appreciable difference (table 19). When the intake of the three "essential" fatty acids is considered, however, a somewhat lower cholesterol level is seen in the group with highest relative intake, whether expressed as per cent of calories or per cent of fat (tables 20, 21). Because the ratio of dietary "essential" fatty acids to saturated fatty acids is thought to be a determinant of blood cholesterol concentration, the sub-

TABLE 19

Mean Total Cholesterol with Per Cent Fat from "U.F.A." and Age

Age	Per Cent Fat from "U.F.A."					
	Less than 55%		55–57.9%		58% and Over	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	16	233	14	227	7	214
30–39	27	244	23	224	23	238
40–50	27	238	25	253	26	248
All ages	71	239	62	236	56	240

jects were subdivided into three groups with different ranges of this ratio, and cholesterol levels of the subgroups were compared. The mean total cholesterol concentrations were practically identical in all groups (table 22).

Dietary cholesterol per se is no longer believed to affect blood cholesterol in man significantly,[22] but because foods rich in cholesterol are, for the most part, also rich in saturated fat, a comparison was made between cholesterol

TABLE 20

Mean Total Cholesterol with Per Cent Calories from "Essential" Fatty Acids and Age

Age	Per Cent Calories from "E.F.A."			
	Less than 5%		More than 5%	
	No.	Chol.	No.	Chol.
20–29	20	229	18	225
30–39	36	240	37	232
40–49	40	250	38	242
All ages	96	242	93	235

intake and serum cholesterol in this group. Table 23 shows that the group with lowest intake had the lowest serum cholesterol, but those with highest intake had somewhat lower serum levels than the group with intermediate intake.

Because those foods richest in saturated fats are also richest in animal protein, and because excessive intake of certain proteins has been implicated

TABLE 21

Mean Total Cholesterol with Per Cent Fat from "E.F.A." and Age

Age	Per Cent Fat from "E.F.A."			
	Less than 13%		More than 13%	
	No.	Chol.	No.	Chol.
20–29	29	232	9	214
30–39	41	235	32	238
40–50	46	250	32	240
All ages	116	240	73	236

in atherosclerosis in animals,[23] subgroups with varying percentages of caloric intake from animal protein were compared in regard to serum cholesterol concentration (table 24). There is a slight trend for higher cholesterol levels in those with relatively greater animal protein intakes, but, as with all the "within group" comparisons thus far, the differences are not significant.

Cigarette smoking has been found in epidemiologic studies to be associated with coronary heart disease, although not so strongly as with lung cancer. The relationship of cigarette smoking to blood cholesterol level in this group is shown in table 25; those who smoke one pack or more per day have an appreciably higher mean serum total cholesterol level than do

TABLE 22

Mean Total Cholesterol with Ratio of "Essential" to Unsaturated Fatty Acids

Age	Ratio "E.F.A."/"U.F.A."					
	Less than .30		.30–.39		.40 and Over	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	20	229	14	235	4	190
30–39	27	237	25	231	21	240
40–50	22	248	36	245	20	248
All ages	69	239	75	238	45	239

the nonsmokers. Is this a direct relationship, or is it due to a common factor, namely, the character of the host himself—that is, the candidate for coronary heart disease?

The mean serum total cholesterol and beta lipoprotein levels of patients with coronary heart disease have been found in most studies to be significantly elevated above the mean level of so-called "normal" control sub-

TABLE 23

Mean Total Cholesterol with Cholesterol Intake and Age

Age	Cholesterol Intake, in mg. per Day					
	Less than 500		500–999		1000 and Over	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	2	203	21	224	15	236
30–39	15	231	43	239	15	234
40–50	9	227	62	249	7	247
All ages	26	227	126	241	37	237

jects. This relationship could not be explored here, for none of the 189 subjects had evidence of coronary heart disease. The one man with possible angina pectoris, although found to have "normal" blood lipid values and a normal electrocardiogram, both while resting and after exercise, was nevertheless not included in the study. Of the 189 electrocardiograms, 159 were interpreted as normal; 19 of the others were "borderline," and 11 were definitely abnormal. The electrocardiographic changes in the main con-

TABLE 24
Mean Total Cholesterol with Per Cent Calories from Animal Protein and Age

Age	Per Cent Calories from Animal Protein					
	Less than 9%		9%–12.9%		13% and Over	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	5	222	26	224	6	241
30–39	18	240	43	235	12	235
40–50	18	239	46	250	14	243
All ages	41	237	115	238	32	240

sisted of abnormally low or flat T waves or prolonged QRS complexes; no tracings suggestive of myocardial ischemia or infarction were seen. Although it could not be proved at this time, it is possible, or indeed probable,

TABLE 25
Mean Total Cholesterol With Cigarette Smoking and Age

Age	Packs of Cigarettes per Day							
	None		Less than One		One		More than One	
	No.	Chol.	No.	Chol.	No.	Chol.	No.	Chol.
20–29	8	230	12	215	10	237	7	233
30–39	21	228	16	234	13	247	17	245
40–50	19	231	21	244	26	257	12	251
All ages	48	230	49	233	49	250	36	245

that underlying coronary heart disease is responsible for at least some of the abnormal electrocardiograms which were found. Such a probability is fairly certain since, according to pathologic studies,[24] the chances are great that not a few of these "normal" subjects, with or without electrocardio-

TABLE 26
Mean Cholesterol Concentration with Electrocardiographic Findings and Age

Age	Electrocardiogram					
	Normal		Borderline		Abnormal	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	28	218.4	4	248.8	6	255.7
30–39	68	234.8	3	281.3	2	208.5
40–50	63	243.3	12	259.3	3	256.0
All ages	159	236.1	19	260.5	11	253.6

graphic abnormalities, have already developed significant, though asymptomatic, coronary heart disease. In table 26 it can be seen that mean cholesterol levels of the groups with borderline and abnormal electrocardiograms are significantly higher than those of the remainder of the subjects.

TABLE 27

Mean Cholesterol Concentrations with Blood Pressure and Age

Age	Blood Pressure					
	Normal		Borderline		Abnormal	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	27	219.5	9	248.8	2	239.0
30–39	54	235.5	13	232.9	5	255.2
40–50	44	234.7	30	260.8	3	283.7
All ages	125	232.6	52	252.3	10	260.0

Elevated blood pressure was likewise found to be positively associated with elevated serum cholesterol (table 27). Here, as with electrocardiographic abnormalities, this relationship is not by virtue of an older age distribution within the abnormal groups, as might be expected, for the 20–29 age group is more strongly represented, and the 40–50 group less strongly represented, than in the group as a whole.

TABLE 28

Mean Total Cholesterol with Pertinent Family History and Age

Age	Number of Familial Diseases*					
	None		One		Two or More	
	No.	Chol.	No.	Chol.	No.	Chol.
20–29	18	222	11	243	9	224
30–39	23	233	31	230	19	250
40–50	26	240	24	237	28	258
All ages	67	232	66	235	56	250

* Diabetes mellitus, arterial hypertension, cerebrovascular accidents, nephritis and coronary heart disease.

As an indication of who among these "normal" men might be more susceptible to coronary heart disease, they were separated according to family history of none, one and two or more diseases thought to be somehow related to coronary disease (diseases so included were diabetes, hypertension, cerebrovascular accident and nephritis), and coronary heart disease itself. Those with a history of two or more such diseases in their families have appreciably higher serum cholesterol than those with none or one (table 28).

Clinical Survey

In the absence of direct and reliable data on prevalence of coronary heart disease among these Italo-Americans, it was considered of interest to determine its frequency among adult Italian males hospitalized in a large Boston general hospital (Boston City Hospital),* and to compare this rate with that reported by White in a similar hospital survey in Naples.[25]

Although it is recognized that to take such comparisons at face value may be open to some criticism, the fact that the data were collected by the same person, namely, P. D. W., in each city, that is, Naples and Boston, using the same criteria, makes the comparison valid. Although it is unlikely that the population of gainfully employed Italian workers in the suburb

Table 29

General-Hospital Survey of Males Aged 40 to 70 to Determine the Incidence of Cases of Coronary Heart Disease

Italians	40–50	50–60	60–70	Total	Per Cent
Naples					
Total	73	94	72	239	3
Coronary	4	1	3	8	
Boston					
Total	41	47	124	212	18
Coronary	5	7	27	39	
Sardinia					
Total	81	39	25	95	4
Coronary	0	3	1	4	
Bologna					
Total	49	65	43	157	13
Coronary	8	7	6	21	
Boston (Mixture of Races)					
Total	38	62	66	166	18
Coronary	8	9	13	30	

of Boston which was sampled in this nutritional study is wholly representative of the population of Italian males who are found in the Boston City Hospital, in which the following record review was carried out, the same situation existed in the investigation conducted in Naples.

A survey was made of the records of 431 adult males with obviously Italian names † who had been hospitalized on the medical wards of the Boston City Hospital during the last year. One hundred sixty-seven of these were over 70 years old and therefore were excluded from analysis because of the age limits of 40 and 70 set for both Naples and Boston.

* We are grateful to Dr. Lawrence Ellis and others of the Boston City Hospital staff for their coöperation in enabling us to analyze the hospital records.

† At least 75% of Italian immigrants who have come to Boston during the last generation are from Naples and the surrounding countryside in southern Italy; the remaining 25% have come from central and northern Italy.

There were 212 Italian males between 40 and 69 years of age among whom it was possible to be quite certain that coronary heart disease did or did not exist. A careful study of the records of these 212 men showed that 39 of them (18%) had been found to have coronary heart disease. This figure of about one fifth stands in marked contrast with that of 3% which was found in the Naples survey, and—with the reservations previously noted—can be taken as an indication that Americanized Italian men do in all probability suffer much more frequent coronary heart disease than do native Neapolitans. A further analysis of these 39 cases by age showed that five of them were in the forties, seven in the fifties, and twenty-seven in the sixties. It is of interest that the percentage (18%) was precisely the same for the Italian patients in Boston as for the patients of all racial origins in the same hospital already reported.

Discussion

In this study we sought to discover whether men of Italian descent living in Boston would have similarly low or higher serum cholesterol levels than would men living in Naples, and to compare the dietary fat intake as well as the cardiovascular status of these two groups.

Although the determination of total cholesterol in the serum is subject to appreciable error,[26] it provided the firmest basis for comparison of the native and Americanized Neapolitans. The Bostonians had significantly higher levels. That this difference is due to environmental factors rather than to a characteristic of the host cannot be doubted. The mean blood lipid levels of these men are very near to those found in other groups living in the American environment by Lawry et al.[26]

Whether diet is the more important environmental factor in relation to these higher levels is less easy to decide, but the fact that the assessed diet of these Bostonians is twice as high in fat as is that of the Neapolitans, plus the frequently observed fact that a mixed diet high in fat elevates serum cholesterol, points to diet as the culprit.

The limitations of the dietary interview as a measure of food intake have been discussed, and the difficulties of measuring other factors of possible importance, such as degree of physical activity and emotional tension, are well known.

The question of whether the higher blood lipids of these Boston-Italians make them more vulnerable to coronary disease can be answered only indirectly and imperfectly, but from other studies showing higher coronary disease rates among groups with higher blood lipid levels, and from our comparison of coronary disease rates among Italian men hospitalized in Boston and Naples, the inference is strong that increased group susceptibility to coronary heart disease does go hand in hand with the elevated blood lipids of these men.

The contrast between the two groups in Boston and Naples in regard

to diet and total serum cholesterol is striking, but comparisons of these factors within the Boston group yielded no definite associations. Those who ate a lesser proportion of calories from fat had slightly higher blood lipids than did those who ate more, contrary to expectations, while those who ate a higher proportion of "essential" fatty acids had a somewhat lower serum cholesterol level, in conformity with current theory. None of the correlations of nutrients with blood lipids was strong, however, nor could they be expected to be, considering the similarity and relatively high fat content of the diets of this entire group of men.

This prospect should be clearly recognized in epidemiologic studies of diet and heart disease. Unless the population to be studied gives promise of considerable internal difference in regard to diet, the effect of diet upon blood lipids or disease cannot be expected to be demonstrated.[27] Such dietarily homogeneous populations can, of course, be compared with other populations, provided similar methods of study are used with each group, or such a population can be studied of itself if it is desired to measure the relationship of certain other factors to disease and to attempt to control dietary factors.

Although in this group of men dietary nutrients appeared to bear no particular relation to blood lipids, certain nondietary factors were found to have varying degrees of correlation with serum total cholesterol concentrations. Chief among these were age and overweight, although lipid levels were no higher with excess obesity than with moderate. Attempts to correlate types of body build or degree of physical activity with blood lipids were unsuccessful. The finding of lower mean serum total cholesterol among the apparently most mesomorphic and masculine males is contrary to expectation based upon observations of higher risk of coronary disease among such men. Nor could the expected correlation between caloric intake, caloric output, and relative weight be demonstrated, doubtless due to inadequacies in method of measuring the first two factors. The apparent paradox of a decreasing caloric intake with increasing weight cannot be adequately explained and may be an artifact, but it is consistent with certain studies [28, 29, 30] which have demonstrated that the caloric intake of the obese person is actually slightly less than that of the nonobese person of the same height, age and sex.

The difference in blood cholesterol level between those who smoked one package or more of cigarettes per day and those who smoked less is considerable. Similarly, those with a strong family history of cardiovascular-renal disease or diabetes, as well as those with elevated blood pressure and nonspecific electrocardiographic abnormalities, also had higher mean levels of serum cholesterol than did those without these findings. It should be emphasized again, however, that analysis of none of these factors or combinations thereof makes possible the prediction of who among these men will develop disease, and further, that association with a certain factor does

not imply a causal relationship. It is planned to follow these men periodically in the future to try to ascertain more adequately the role of these various factors in the natural history of coronary heart disease among them.

Summary

One hundred eighty-nine healthy Boston men, aged 20 to 50, whose parents had been born near Naples but who themselves had lived all their adult lives in the United States, were found to have a mean serum total cholesterol level and dietary fat intake similar to that of other Americans, and significantly higher than that of native Neapolitans.

Their likelihood of developing coronary heart disease was assessed indirectly by comparing the frequency of arteriosclerotic heart disease among male patients, aged 40 to 70 years, hospitalized in Boston and Naples, with a rate of 18% for the Boston City Hospital and 3% in Neapolitan hospitals.

Internal comparison of the Boston group revealed no significant differences in the mean blood lipid levels of subgroups when segregated according to differences in per cent of dietary calories from fat, from unsaturated fatty acids, from "essential" fatty acids, or from animal protein. The range of intake of these nutrients did not vary greatly among this group, so that failure to find positive correlations does not prove that such correlations would not exist when comparing groups with greater contrast in dietary patterns.

When the group was segregated according to ranges of age, relative body weight, cigarette smoking, blood pressure, electrocardiographic findings and family history of cardiovascular-renal disease or diabetes, appreciable differences in mean blood lipid levels were found.

Summario in Interlingua

Le hypothese que le ingestion de quantitates excessive de grassia dietari es un causa de morbo de arteria coronari e de morbo cardiac ha le supporto de multe indicios suggestive, sed su demonstration per provas rigorose ha non ancora essite effectuate. In recente annos, investigationes epidemiologic ha devenite plus commun con respecto a morbo cardiovascular, e le reportos de multe tal investigationes reinfortia le hypothese de "hyperlipemia ex hyperlipophagia" como causation de morbo cardiac coronari. Keys et al. reportativa que obreros neapolita, le dietas de qui contine approximativemente 20 pro cento de grassia (in terminos caloric), ha plus basse nivellos de cholesterol del sero e un plus basse incidentia de morbo cardiac que simile gruppos de obreros in le Statos Unite, ubi le dietas contine circa 40 pro cento de grassia.

Pro determinar additionalmente si factores ambiental e constitutional es plus importante con respecto al basse nivellos de lipido sanguinee que esseva observate in ille neapolitas e pro evalutar meticulosemente le habitudes dietari e le stato cardiovascular de un comparabile gruppo de masculos habitante le Statos Unite, le observationes del presente reporto esseva facite in un gruppo de membros del prime generation american de familias neapolita.

Cento octanta-nove masculos bostonian in bon stato de sanitate, de etates de inter 20 e 50 annos, con parentes nascite in le vicinitate de Neapole, sed qui illes

mesme habeva passate omne lor vitas adulte in le Statos Unite, esseva studiate con le constatation que le valor medie de lor cholesterol total del sero e lor ingestion dietari de grassia es simile a lo que vale pro altere americanos e significativemente plus alte que le valores valente pro neapolitas native.

Le question del disveloppamento probabile de morbo cardiac coronari esseva attaccate indirectemente per comparar le frequentia de morbo cardiac arteriosclerotic in le patientes mascule de etates de inter 40 e 70 annos in Boston con constatationes correspondente in Neapole. Iste incidentia esseva 18 pro cento al Hospital Municipal Boston e 3 pro cento in le hospitales de Neapole.

Intra le gruppo de Boston, nulle significative differentias del nivellos medie de lipido sanguinee esseva constatate in le comparation de subgruppos segregate super le base de differentias del procentages del calorias dietari representate per grassia, non-saturate acidos grasse, acidos grasse "essential," o proteina animal. Le ingestion de iste nutrientes non variava grandemente intra le gruppo total, de maniera que le absentia de correlationes positive non exclude le possibilitate de lor existentia in le comparation de gruppos con plus acute contrastos del modos dietari.

Quando le gruppo total esseva subdividite secundo le criterios de etate, de peso relative del corpore, de fumar o non-fumar cigarrettas, de pression de sanguine, de constatationes electrocardiographic, e de presentia o absentia de historias familial de morbo cardiovascular e renal o de diabete, differentias appreciabile del valores medie de lipido sanguinee esseva trovate.

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MYOCARDIAL METABOLISM * †

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For many years the study of cardiac metabolism has been of concern primarily to the physiologist working on the isolated heart and to the biochemist interested in the general aspects of intermediary metabolism.[1, 2, 3, 4, 5, 6, 7] Recently, the subject has also come to the attention of the surgeon and of the internist.[8] The former has had to concern himself with the oxygen consumption and the efficiency of the arrested heart during cardiac surgery, while the internist has begun to think about the heart muscle in its relation to congestive heart failure and coronary occlusion.[9, 10] In addition, the survival of the heart during complete or partial ischemia, either artificially induced during cardiac surgery or occurring during coronary occlusion, has focused attention on the resistance of the heart to anoxia.[11] The present discussion is concerned with a review of cardiac metabolism of the beating and the arrested heart; it will also deal with disturbances of cardiac metabolism in congestive heart failure and in myocardial ischemia and anoxia.

Metabolism of the Arrested and Fibrillating Heart

Cardiac Efficiency: The estimation of mechanical efficiency of an organ represents an important criterion in evaluating the degree of functional integrity. Efficiency is represented as the ratio of the thermal equivalent of the work performed and of heat liberated.[11] In the case of the heart, it may be indirectly calculated by comparing the work performed with the myocardial oxygen usage. The former is synonymous with energy utilization, while the latter represents total energy production. Determination of myocardial efficiency from the oxygen consumption of the heart cannot be made unless one is sure that anaerobic glycolysis in heart muscle is absent. An additional difficulty in the calculation of myocardial efficiency arises from the fact that these calculations are valid only as long as the energy produced, aside from being degraded into heat, is utilized exclusively for "useful work." [11] This represents only the mechanical work expended by the heart in overcoming the resistance in the systemic and pulmonary cir-

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culations and in imparting momentum to the blood. Therefore, a knowledge of the oxygen consumption of the nonbeating heart is essential in the determination of myocardial efficiency. In the presence of constant external work, the efficiency of the beating heart depends to a large extent upon the oxygen consumption of the arrested organ.[12] As indicated above, oxygen and substrate utilization by the arrested heart is also of interest to the cardiac surgeon. With the use of specially devised technics which permit the determination of the oxygen consumption of the arrested dog's heart with the chest closed, it has been demonstrated that the oxygen usage of the heart arrested with potassium chloride varies between 20 to 35% of that of the naturally perfused heart in situ (table 1).[13] This finding is in agreement with results obtained by Gregg and his co-workers [12] on the dog heart and with those of Clark on the frog heart.[14] When the frog heart is arrested, the oxygen consumption is also reduced to 20% of the ordinary working value.[14] A comparison can also be made between the oxygen consumption

TABLE 1

Comparative Oxygen Consumption of Heart Slices and Hearts in Situ

Preparation	Q_{O_2} (Left Ventricle)
Tissue slices (rat)	3.5
Arrested dog heart	10.0
Beating dog heart	54.0
Beating human heart	25.4

of tissue slices and of the arrested heart in situ. This necessitates conversion of myocardial oxygen usage into units of dry weight, which can be accomplished by a factor (5.22) representing the relationship between dry and wet weight of tissue slices.[11] The results of these calculations are presented in table 1. It can be seen that, per unit of weight, the arrested dog heart possesses a considerably larger oxygen consumption than rat heart muscle slices respiring in the Warburg apparatus.[15] With the use of this technic it was also shown that there is no significant difference between the oxygen consumption of the fibrillating heart and the heart arrested with potassium chloride.[15]

The relatively high oxygen consumption of the arrested perfused heart necessitates a reëvaluation of previously published data on myocardial efficiency. Such calculations can now be made from the difference in myocardial oxygen usage between the naturally beating and the arrested dog's heart (mean oxygen usage of the beating heart is 25.1 ml./minute, that of the arrested heart is 4.83 ml./minute). Accordingly, 19% of the total oxygen consumption of the left ventricle is used for "basal metabolic" processes exclusive of work. The efficiency of muscular activity of the heart can then be calculated by making allowances for the oxygen consumption of the arrested heart. Therefore, myocardial efficiency is approximately 37% in the dog and 39% in man. These figures are much higher than those

previously published from this laboratory because the oxygen consumption of the arrested heart was not considered.[16, 17]

The introduction of a method to measure the oxygen consumption of the normally beating heart, the empty beating heart, and the arrested and fibrillating organ of closed chest dogs has made it possible to study the survival of energy production in the whole heart after interruption of the coronary circulation.[18] The arrested heart was artificially perfused in situ following varying intervals of interruption of the coronary circulation.[18] Results obtained with this technic were compared with those in which the oxygen consumption of heart muscle slices was determined in the Warburg apparatus. The results of these observations can be seen in figure 1. The

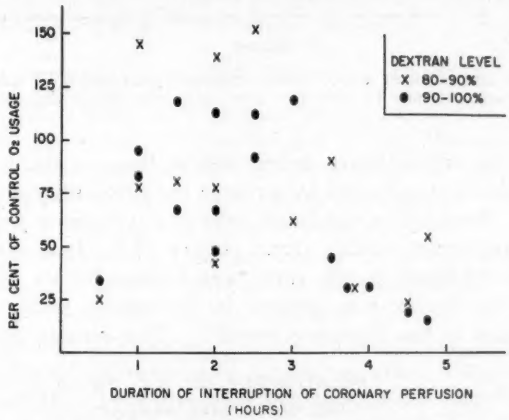

FIG. 1. The relationship of duration of interruption of coronary perfusion through the arrested heart in situ to the percentage of control oxygen usage. Only data were selected in which recovery of dextran in coronary sinus blood was above 80%, in order to eliminate admixture of blood appearing in the coronary sinus originating from the ventricular cavities. It may be seen that the control levels of oxygen usage were maintained for about two and one-half hours; longer interruption of perfusion resulted in a decline in myocardial oxygen usage.

oxygen usage of the arrested whole heart in situ remains at control levels if the interruption of the coronary circulation does not exceed two hours. Longer interruptions of perfusion result in rapid diminution of myocardial oxygen usage; after ischemia of from four to five hours, myocardial oxygen consumption ceases.[15] Interruption of the coronary circulation results in significant disturbances in the myocardial extraction of carbohydrates—for example, myocardial lactate and pyruvate production increases.[15] After four hours of complete myocardial ischemia, myocardial oxygen usage declined proportionately more than myocardial glucose usage, probably as a result of anaerobic glycolysis. In heart muscle slices obtained from dogs at varying intervals after death, a much more rapid decline in oxygen consumption could be demonstrated than had been observed in the whole heart (figure

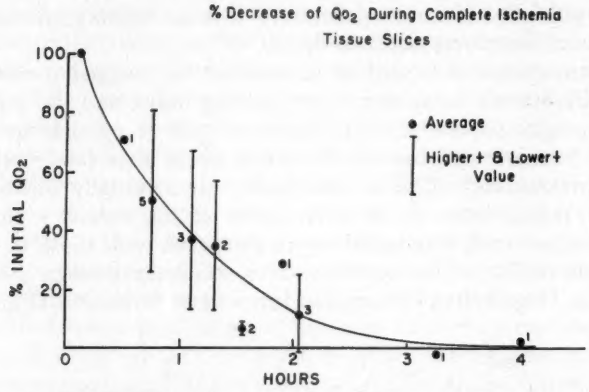

FIG. 2. The Qo_2 of heart muscle slices removed from hearts of animals at varying intervals after death. It may be seen that one hour after death only 40% of the initial Qo_2 remains.

2).[15] As in the whole heart, heart muscle slices respond to anoxia by glycolysis. This was indicated by a rise in the respiratory quotient of these slices to 1.4. There was a significant relationship between the height of the RQ and the duration of cardiac arrest (figure 3).[15] It is likely that lactate production by the heart muscle slices was responsible for the elevation in the RQ, and that lactate was released by the muscle under aerobic conditions which exist in the Warburg vessel.[15] This aerobic glycolysis is evi-

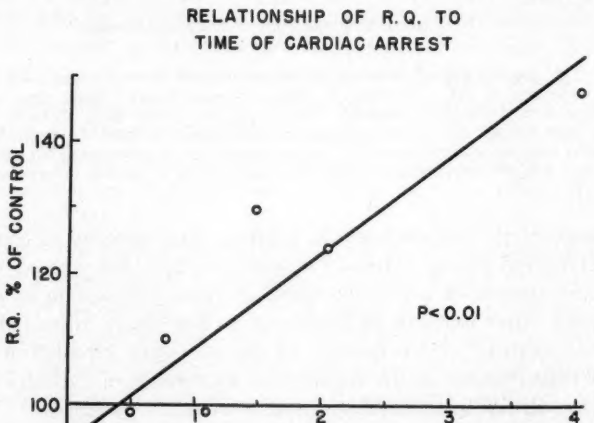

FIG. 3. The positive relationship between respiratory quotient (expressed in per cent of control value) of heart muscle slices and the time after death at which the slices were prepared. The rise in respiration quotient is probably the result of release of lactic acid into the buffer solution.

dence of the severe metabolic damage incurred during the prolonged period of anoxia. These results are in agreement with those of Fuhrman and associates, who exposed heart slices to complete anoxia; they observed that these preparations failed to regain their previous rate of oxygen consumption, possibly due to destruction of essential enzymes.[18]

The results on the arrested heart may be summarized as follows: The arrested heart uses about 25% of the oxygen consumption of the beating heart; there is no difference in the oxygen utilization of the fibrillating, the arrested, or the empty beating heart; the efficiency of the heart is much greater than had been previously estimated; the oxidative enzymes of the heart possess a considerable resistance to anoxia; finally, aerobic glycolysis does take place in the heart muscle in the presence of oxygen, provided this has been preceded by a period of myocardial anoxia.

Energy Production in the Normally Beating Heart

Studies concerned with the utilization of oxygen and of substrates by the whole heart originated in the early part of the 20th century, in both cold-blooded and mammalian hearts. Extensive work has been performed on the metabolism of the beating heart. The pioneer studies were undertaken by Clark [19] and by Starling and their co-workers.[1] Clark's work on the perfused frog heart suggested that this organ can oxidize glucose, lactate, amino acids and fatty acids.[19] Studies on the metabolism of the isolated dog's heart in the heart-lung preparation were initiated by Starling and Evans.[1, 2] They showed that the RQ of the heart-lung preparation was about 0.85, suggesting utilization of substances other than carbohydrates. Visscher et al. found that the carbohydrates used by the heart were sufficient to account for only 20% of the total cardiac oxygen consumption.[3] Others came to similar conclusions from the observation that the RQ was less than unity.[20] Evans and his co-workers, among others, showed that the myocardial usage of lactate and glucose accounted for only 60% of the total cardiac oxygen consumption.[21] Braun-Menéndez demonstrated the myocardial usage of pyruvate.[22] Clark and co-workers found that the frog heart deaminates and oxidizes amino acids; however, Cruickshank et al., working on isolated dog's heart, could not confirm this.[19, 23]

Introduction of the nitrous oxide method by Kety for the determination of cerebral blood flow in 1945 and of the catheterization of the coronary sinus of man in 1947 has made it possible to measure coronary blood flow in the intact heart in situ and to study the myocardial extraction of substrates and oxygen.[24, 25] It was found that the human and dog hearts utilize considerable quantities of fatty acids, ketone bodies and amino acids (table 2). Definitive proof of the usage of fatty acids by the human heart has been obtained in tests in which the fatty acid levels in blood were increased by a high fat intake.[16, 17, 26] In these patients the contribution of fatty acids to the oxygen usage of the heart (the myocardial oxygen extraction ratio) was

frequently above 100%, and statistical analysis confirmed the difference between patients in the postabsorptive state and after ingestion of fatty acids. It is likely that this increase in the apparent usage of fatty acids by the heart represents storage of fat in heart muscle.[16, 17, 26]

The great avidity of the heart for fat may have far-reaching implications, transcending the importance of fatty acids as an important fuel for energy production by the heart muscle. Lipids may reach the heart as unesterified fatty acids or as triglyceride-rich lipoproteins. It has been proposed that unesterified fatty acids represent the blood lipid fraction which is immediately available to the cells in general as a supply of lipid to meet the energy demands.[27] As mentioned above, the myocardium of the fasting subject derives a major share of its energy from unesterified fatty acids.[26] Anfinsen has demonstrated that the fatty acid level of blood entering the myocardium is markedly decreased following glucose administration, and that simultaneously the extraction of unesterified fatty acids by the heart ceases.[28]

TABLE 2

Relative Contribution of Carbohydrates and Non-Carbohydrates to Total Myocardial Oxygen Usage

Carbohydrate	%	Noncarbohydrate	%
Glucose	17.90	Fatty acids	67.0
Pyruvate	0.54	Amino acids	5.6
Lactate	16.46	Ketones	4.3
Total	34.90%	Total	76.9%

According to this author, the counteracting effect of glucose on fatty acid utilization appears to take place at the site of liberation of unesterified fatty acids into the blood. It is likely that transport mechanisms for lipid as unesterified fatty acids are under hormonal control and involve a lipoprotein-lipase system which is sensitive to antiheparin agents.[29] Work is needed to study the hormonal control of fatty acid utilization by the heart and to investigate possible myocardial utilization of triglyceride-rich lipoproteins. A connection between these findings and atherosclerosis of the coronary arteries has as yet not been established, but the subject deserves further attention.

Finally, the work of Clark in 1914 has suggested that phospholipid substances may be concerned in maintaining the contractility of the heart.[30] Clark found that the frog heart perfused with Ringer's solution becomes hypodynamic, and that normal contractility can be restored by the addition of saponified serum lipids to the perfusion fluid. Hadju and his co-workers have recently identified such a substance in blood as beta-palmitoyl lysolecithin.[31] However, the physiologic importance of this and related compounds has not been ascertained.

Ketones are utilized by the human and the dog heart; their aerobic metabolism accounted for approximately 5% of the total myocardial oxygen

extraction.[16, 26] In contrast to the heart-lung preparation, the human and the dog hearts in situ extract considerable quantities of amino acids from the coronary blood. After infusion of amino acids, as much as 40% of the total cardiac oxygen consumption can be accounted for by aerobic metabolism of amino acids. A small rise in arterial amino acid concentration of 20% produces a disproportionate increase in the myocardial extraction of 245%. The high uptake of amino acids by the heart does not indicate storage, as in the case of fatty acids or glycogen. Oxidation of amino acids probably leads eventually to the formation of some member of the citric acid cycle furnishing high energy phosphate to be utilized for muscular contraction. Amino acids may also form glycogen, which can be stored to be used later for the production of energy. Finally, amino acids may be transformed into other nitrogenous compounds and find their way not only into other amino acids but also into the whole protein structure.

Total utilization of carbohydrates covers only approximately 35% of the total energy production of the heart (table 2).[16, 17] It has become apparent that both myocardial glucose and lactate usages are functions of their respective arterial concentrations. At low arterial glucose concentrations (below 80 mg.%) the coronary arteriovenous glucose difference is usually less than 4 mg./100 c.c. At normal blood concentrations, glucose and lactate are used by the human heart in approximately equal amounts. Similarly to the perfused dog's heart, the human heart appears to utilize pyruvate.

The results obtained on the beating human heart in situ show that fatty acids contribute more to myocardial energy metabolism than does any other substrate. In addition to fatty acids, the heart can utilize glucose, pyruvate, lactate, ketones and amino acids.

Myocardial Metabolism in Diseases of the Heart

It is difficult to localize disturbances in heart muscle which accompany or result in heart disease. Biochemically, electron transport, citric cycle oxidation and oxidative phosphorylation are all aspects of a single problem.[7] These mechanisms are parts of individual but highly integrated units, and none of these mechanisms can be understood without references to the other concomitant processes.[7] In order to deal with these functions, structural and functional relationships should be correlated. In addition, it is impossible to separate muscular contraction from the structural and biochemical processes taking place in mitochondria and their subdivisions. Energy production and utilization are inseparable. The technic that can be used to investigate metabolism of the beating heart in situ is not adequate to pinpoint the location of the defect underlying disturbed cardiac functions.[25, 32] However, although one must not expect an answer as to whether oxidative phosphorylation, electron transfer system or the enzymes of the citric acid cycle are responsible for specific disturbances of cardiac function, serious

interference with any of these functions may alter the over-all pattern of myocardial metabolism and may be reflected in changes of myocardial oxygen consumption or utilization of substrates. For example, a substantial increase in the specific rate of oxidation of the heart may signify diminished capacity for oxidative phosphorylation. This process acts as a brake on the speed of oxidative processes which, when released, leads to a considerable increase in the rate of oxygen consumption.[7] The appearance of increased amounts of lactate or pyruvate in coronary vein blood suggests glycolysis in the heart muscle, and diminished contractility of actomyosin indicates alterations in the contractile elements of heart muscle.[33, 34]

Myocardial Metabolism in Diabetes

It could be demonstrated during the early phase of investigations of cardiac metabolism on the heart-lung preparation that the diabetic heart metabolizes sugar. With the use of the hearts of depancreatized dogs, a positive myocardial glucose balance was found.[35] In tissue slices obtained from the hearts of diabetic dogs, diminished utilization of pyruvate and lactate was noticed. Similarly, diminished utilization of C^{14}-labeled pyruvate was observed in both cardiac and diaphragmatic muscles of diabetic animals; the fraction of pyruvate converted to CO_2 was decreased. Myocardial utilization of fatty acids was also diminished. This may be related to the disturbances in carbohydrate metabolism, since the transfer of energy required for fatty acid synthesis seems to be derived mainly from coupled reactions involving the simultaneous oxidation of some carbohydrate intermediate. In studies on man, deficient protein synthesis in diabetes was found, since high fasting plasma amino acid levels were frequently present in patients with severe, untreated diabetes.

Coronary sinus catheterization has made it possible to investigate over-all metabolic changes of the diabetic heart in patients with diabetes mellitus and in dogs made diabetic with alloxan.[35] The results obtained with this technic show that myocardial usage of carbohydrates is reduced and that utilization of noncarbohydrate material is increased. The decreased ability of the diabetic human and dog's heart to utilize lactate is particularly conspicuous. The marked reduction of myocardial usage of lactate is primarily responsible for the reduction in the total amount of energy available from the carbohydrate fraction. In the face of reduced carbohydrate utilization, a relatively large amount of noncarbohydrate material must be used by the heart for energy production. This is the case since the hearts of patients with diabetes mellitus extract a significantly greater amount of fatty acids than does the nondiabetic heart. Whether this represents storage or actual utilization of fatty acids is a moot point. The use of ketone bodies by the diabetic heart is also increased.

Insulin leads to a relative increase in myocardial utilization of fatty acids

and ketones.[35] The hormone results in a significant fall in blood sugar, but this occurs without changes in myocardial usage in the extraction of glucose. This implies that insulin causes a relative increase in myocardial glucose utilization. The hormone fails to correct the metabolic defect responsible for diminished myocardial lactate usage. (Arterial lactate concentrations rose, but myocardial extraction of lactate did not change.)

The results obtained on the diabetic heart in situ demonstrate a great variety of metabolic defects. The diabetic heart is deficient in glucose, pyruvate and lactate utilization. In addition, the defect extends to the metabolism of protein and fat. It is unlikely, however, that these diffuse changes in energy production result in disturbances in energy utilization of the heart. The fundamental importance of diabetes in cardiology does not rest on primary metabolic disease of heart muscle, but rather on the frequency with which diabetes results in coronary vascular changes and their complications.

Congestive Heart Failure in Man

Demonstration that catheterization of the coronary sinus can be carried out on the human subject without danger has provided a means of conducting metabolic studies on the hearts of individuals suffering from congestive heart failure.[9] This is particularly useful since congestive heart failure cannot be reliably reproduced in the experimental animal. Studies on these patients have revealed no significant alterations in myocardial oxygen consumption or in the utilization of glucose, pyruvate, lactate, fatty acids, amino acids and ketones by the heart.[9] No evidence of anaerobic metabolism in hearts of patients suffering from congestive heart failure has been noted. It must therefore be concluded that in heart failure there is no difference in energy production per equal weights of cardiac muscle. The failing heart must therefore be deficient in its ability to utilize energy for effective muscular contraction even under basal conditions, since the mechanical work performed is normal or decreased.

The question arises whether the deficiency resides in the production or release of high energy phosphate or within the contractile proteins of heart muscle. Results relating congestive heart failure to a deficiency in the formation of high energy phosphate have been conflicting. Wollenberger found that the spontaneously failing heart in vitro (the heart-lung preparation) retains its normal ATP content and is even richer in phosphocreatine than is the nonfailing heart.[36] On the other hand, Lamprecht et al. demonstrated that, in experimentally produced failure in the dog, the formation of high energy phosphate per unit of oxygen consumed (the p/o ratio) was diminished.[37] The oxygen uptake of sarcosomes is increased during insufficiency, while the phosphate uptake is markedly reduced. It is difficult to reconcile these various results unless one assumes that "heart failure" is the end stage of many different processes, all leading to deficient emptying of the heart as a result of reduced contractility.

Studies on the contractility of actomyosin, the contractile protein of heart muscle of normal and failing human hearts, suggest that in human heart failure the disturbance is localized in the contractile elements.[38] Thus, actomyosin bands prepared from failing human hearts demonstrate a marked diminution in contractility. It is not possible to state at this point what changes in the contractile protein are responsible for diminished contractility. However, it has been previously noticed that in dogs with experimental heart failure there occurred a decrease in concentration of actomyosin, diminished viscosity per unit of actomyosin, and decreased viscosity of response to the addition of ATP.[39] This was ascribed to alterations in the organization of actomyosin, more specifically to the presence of myosin not combined with actin. The dissociated state of actomyosin may be due to physical changes in heart muscle.

"Heart Failure" in the Heart-Lung Preparation: Until the advent of coronary sinus catheterization in man, heart failure was studied only in the isolated heart-lung preparation. It has been noted since the early work of Starling and his associates that the mechanical efficiency of the isolated heart was low (from 3 to 17%). As mentioned in the previous paragraph, the mechanical efficiency of the naturally perfused human and dog heart in situ is about 25% without correcting for the oxygen consumption of the nonbeating arrested heart. In addition, work on the isolated heart has demonstrated that spontaneous insufficiency of the heart occurs within hours after separation of the heart and lung from the rest of the organism.[4] It has been repeatedly shown that this spontaneous insufficiency of the isolated heart is accompanied by an increase of the myocardial oxygen consumption per unit of work, that is, by a decline in the mechanical efficiency. Rein has indicated that this decline in the mechanical efficiency of the isolated heart commences immediately after isolation of this organ.[40] As Rein has shown, this loss in efficiency is not the result of a diminution in fuel supply of the perfusate, but depends upon the continuity between the heart with the rest of the organism.[40] When the liver was excluded from the circulation prior to the isolation of the heart, the fall in the myocardial efficiency was much more precipitous. These observations suggest that small amounts of blood coursing through the liver may be sufficient to maintain normal myocardial efficiency. Rein made the additional observation that the circulation through the hepatic artery was of particular importance.[40] He also found that the protective influence of the liver became more conspicuous during anoxemia. He finally concluded that, in addition, splenectomy lowered the resistance of the heart to increased load and anoxemia. He therefore postulated that the spleen, upon nervous stimulation, released a substance which is responsible for the secretion of the final cardiotonic agent.[40]

Experiments undertaken in this laboratory reveal that in certain respects the metabolism of the isolated heart differs from that of the naturally perfused organ in situ. For example, the oxygen consumption of the isolated

heart is significantly reduced.[41] However, even in the presence of marked spontaneous insufficiency, the myocardial extraction of glucose, pyruvate and lactate remains unaltered despite a significant diminution in the work of the heart and a decline in myocardial efficiency.

The diminution in myocardial oxygen consumption differentiates the metabolism of the spontaneously failing heart in the heart-lung preparation from that of the failing human heart. The cause for the diminished efficiency of the isolated heart is not understood.

Conditions Which Result in Production of Lactate by the Heart Muscle

The appearance of increased amounts of lactate is not of necessity the result of inadequate cellular oxidation; it is also demonstrably affected to a very significant extent by changes in pyruvate concentration resulting from overventilation or pH alterations, or by changes in blood glucose concentration. Lactate accumulation ensues as a result of its tendency to maintain equilibrium with the pyruvate present.[42] However, in heart muscle, anaerobic metabolism is a likely explanation for the observation of an increase in coronary vein lactate concentration above that of arterial blood (negative myocardial lactate balance). Hyperventilation does not occur in experimental embolization of the coronary arteries where lactate production by the heart is immediate and is at first restricted to the heart muscle alone.[10] There is also no immediate change in glucose concentration in blood.[10] It is likely, however, that under certain circumstances the production of lactate by the heart muscle may not be the result of anaerobiosis.

Myocardial Infarction and Hemorrhagic Shock: When embolization of the coronary arteries is experimentally produced in the closed-chest dog by injection of microspheres suspended in blood plasma, there occurs an almost immediate increase in the concentration of pyruvate and lactate in coronary vein blood.[10, 43] The production of these substrates by the heart contrasts with the continued myocardial usage of glucose; this is probably due to the fact that anaerobic glycolysis proceeds in heart muscle under these conditions. These metabolic changes, however, are rapidly reversible, and 20 minutes following embolization of the coronary arteries myocardial utilization of carbohydrates has returned to normal.[10] After approximately five hours, plasma activity of enzymes such as oxalacetic acid transaminase, phosphohexoisomerase, fructose aldoase and malic acid dehydrogenase is increased. The peak of activity of these enzymes occurs 24 hours after embolization, and correlates well with the height of coagulation necrosis of the myocardium.[10] As regenerative processes take place, plasma activity of these enzymes decreases.[10, 44] It is likely that these biochemical disturbances are initiated by the myocardial ischemia produced by mechanical blockage of some of the coronary vessels. This leads to immediate though fleeting changes in the utilization of substrates by the heart.

In contrast to these changes in substrate utilization by the heart, coronary embolization produces no changes in the coronary arteriovenous difference of diphosphopyridine nucleotide, triphosphopyridine nucleotide, amino acids and amino sugars.[45] The likelihood exists that these negative results are due to the fact that, although the methods of analysis are extremely sensitive, the analytic error is still too great. In addition, substances of small molecular weight are metabolized and excreted at a higher rate than are larger protein molecules. Their accumulation in blood is prevented, therefore, in contrast to the protein enzymes, which are readily detected following myocardial infarction.

In experimental hemorrhagic shock the coronary blood flow is markedly diminished, during both the oligemic and the normovolemic phases.[43, 46] This may result in a significant reduction in the myocardial oxygen usage during both the oligemic and the normovolemic phases of shock. Myocardial pyruvate extraction is usually diminished, and frequently the pyruvate concentration in coronary vein blood exceeds that in arterial blood.[46]

TABLE 3

Results Obtained on the Heart-Lung Preparation

	In Situ	Heart-Lung Preparation
Myocardial oxygen usage	15.56 c.c./100 gm./min.	5.22 c.c./100 gm./min.
Left ventricular efficiency	28.05%	7.7%
Oxygen extraction ratio of:		
Glucose	31.4%	36.1%
Pyruvate	1.16%	2.26%
Lactate	31.6%	33.2%
Ketones	5.1%	4.8%

The metabolic changes observed in the conditions described here follow a certain definite pattern. In congestive heart failure in man, metabolic changes are absent and the myocardial oxygen consumption is normal. In spontaneous heart failure in the heart-lung preparation, myocardial oxygen consumption and efficiency are diminished but the contribution to the myocardial oxygen extraction of substrates (the oxygen extraction ratio) remains unchanged (table 3).[41] In experimental myocardial infarction and in hemorrhagic shock, on the other hand, the heart muscle releases lactate and pyruvate into the coronary vein blood. The same observation was made after interruption of the coronary circulation for varying periods of time. To date, coronary sinus catheterization has failed in the detection of metabolic alterations in heart muscle cells which would either precede cell death or take place in cells in which metabolic changes are reversible. Future studies of myocardial metabolism will probably be directed toward a combination of metabolic balance studies utilizing coronary sinus catheterization and enzymatic studies on heart muscle slices. This can best be accomplished by the use of radioisotopes.

SUMMARIO IN INTERLINGUA

Le studios reportate concerne le metabolismo del arrestate, del fibrillante, e del naturalmente perfundite corde canin e human. Le corde arrestate usa circa 25% del oxygeno usate per le corde naturalmente perfundite. Es a constatar nulle differentia inter le corde fibrillante, le corde arrestate, e le battente corde non-perfundite quanto al grado del utilisation de oxygeno. Le efficacia del corde es multo superior a lo que esseva previemente estimate. Le enzymas oxydative del corde possede un considerabile grado de resistentia contra le effectos de anoxia. Finalmente, glycolysis aerobie occurre in le musculo cardiac in le presentia de oxygeno, providite que isto es precedite per un periodo de anoxia myocardial.

Le resultatos de studios metabolic in le corde human a pulso normal indica que acidos grasse contribue plus al metabolismo de energia in le myocardio que non importa qual altere substrato. A parte le acidos grasse, le corde pote utilisar glucosa, pyruvato, lactato, cetones e amino-acidos.

Le grande aviditate del corde pro grassia es possibilemente de vaste signification, multo in ultra del importantia de acidos grasse como combustibile pro le production de energia per le corde.

Es discutite studios del metabolismo myocardial in varie morbos, incluse diabete, congestive insufficientia cardiac, infarcimento myocardial, e choc hemorrhagic.

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CASE REPORTS

DYSCHONDROPLASIA WITH MULTIPLE HEMANGIOMATA (MAFFUCCI'S SYNDROME) *

By KURT MARBERG, M.D., FRITZ DALITH, M.D., and HARRY BANK, M.B., Ch.B., *Tel-Hashomer, Israel*

A CASE of dyschondroplasia with multiple hemangiomata—Maffucci's syndrome—recently came under our observation. We believe this to be the thirty-fifth case to be described in the literature. The syndrome has been well summarized by Carleton et al.,[1] Bean [2] and Aimes.[3] The rarity of the condition in itself justifies its being reported, and we feel that some features of this particular case, apparently less well known, may be of some importance to those interested in developmental abnormalities.

CASE REPORT

A 40 year old single female, born in Iraq, was admitted because of fever and a skin rash on the left breast for the last three days. Because of the obvious deformities of the skeleton and skin (figure 1), interest was aroused and the following particulars regarding her past history were obtained:

Both parents were healthy and without obvious deformities. A brother and two sisters were similarly healthy and normal in stature, a fact which was substantiated by later examination of the brother.

At birth, which appears to have been normal, and up to the age of eight years, the patient did not present obvious signs of retarded development or any other features of disease.

Her first recollection of any abnormality was at this age, when she fell and fractured her left arm. She could not clearly recall the further development, either of the skeletal deformities or of the appearance of the skin tumors, but stated that as far as she could remember (since approximately the age of 12 years) she had been conscious of being small and of not having grown further.

At various times the patient had had skin rashes, usually painless and not associated with major constitutional symptoms.

In 1935 a painful nodule was removed from the right buttock. The patient recalled no other diseases except an attack of malaria. Menses had started at the age of 12 years and ceased four months prior to her admission.

Examination: The patient was in a good nutritional state, weighing 47 kilos, and measuring 146 cm. Her facial features were normal. Despite the small stature and the skeletal deformities she did not give the impression of being dwarfed. She appeared to be alert. Examination of the heart and lungs was normal. Except for a palpable and firm spleen there were no other findings on examination of the

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abdomen. There were no ocular disturbances, and examination of the nervous system was normal. The left breast was markedly larger than the right. The nipple was retracted, and a firm, painless, diffuse mass could be felt in the depth behind the areolar region.

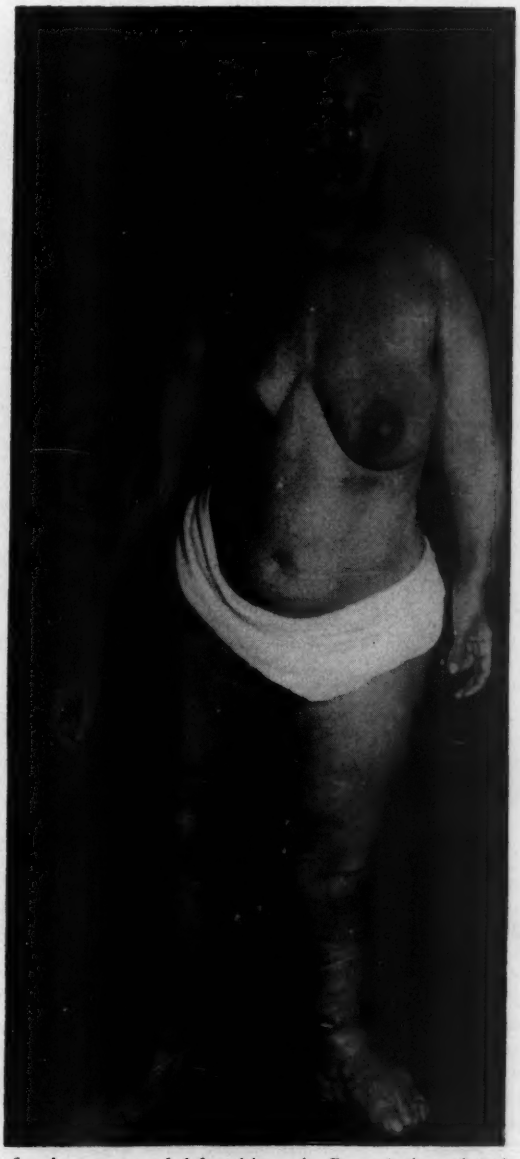

FIG. 1. Appearance of deformities. A. General view of patient.

The particular features presented by the patient are described under changes of skeleton, skin and mucous membranes.

1. Skeletal Changes: The left forearm was 8 cm. shorter than the right. There was a moderate bowing of the radius and ulna. The left upper arm was 1 cm. shorter than the right. The left thigh was 4 cm. shorter than the right, and the left leg 11 cm. shorter than the right. There was a pronounced tilting of the pelvis upward on the right side. The gross deformity of the hands was caused by multiple swellings on the phalanges of different sizes which were attached to the bones.

FIG. 1B. Hands.

Smaller swellings were found on the toes of the left foot. Multiple nodular bony excrescences could be felt through the skin over the right lower part of the thorax and the edge of the left scapula.

2. Skin Changes: The lesions found can be divided into three types. The first consisted of phlebectasias, especially of the veins of the left leg and foot, with resultant gross distortion of the whole limb. These were especially marked on the lateral and medial margins of the foot, where numerous convoluted venous swellings gave the appearance of a grapevine. On the left foot bluish swellings were diffusely scattered; some were firm and painful, some soft and tender. Stony hard concrements could be palpated in some of the nodes. In contrast, the right foot retained its normal shape except for crowding of the lateral three toes due to hemangiomatous swellings at their bases.

The second type of skin lesion consisted of soft, elastic swellings of varying sizes scattered over the body (chest, buttock, limbs), conforming more to the usual hemangioma. On the skin of the perineum there were a few pedunculated swellings, varying in size from a bean to a walnut.

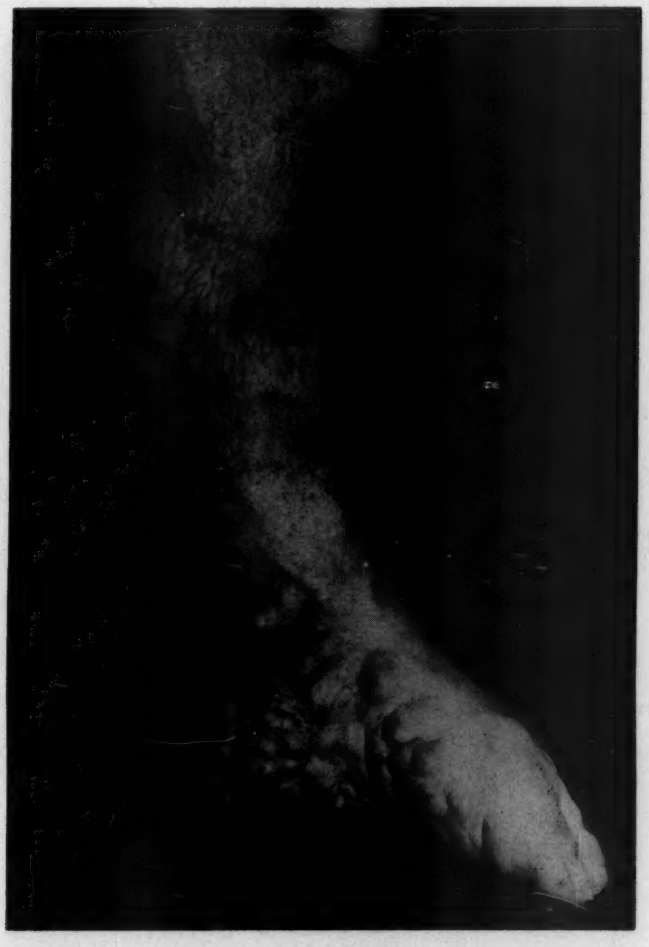

FIG. 1C. Left leg.

The third type of skin lesion consisted of skin discolorations of various kinds. The rash on the left breast found on admission was maculopapular and erythematous, and subsequently vesicular. On its disappearance it left a residual brownish discoloration, slightly elevated and rough to the touch. On the thorax and abdomen there were scattered pigmentations, partly bandlike in distribution, and similar in appearance to the final stages of the breast rash.

3. Mucous Membrane Changes: In the midline of the dorsum of the tongue there was a firm pedunculated violaceous swelling. On the left side of the tongue was a similar but softer swelling, and on the ventral aspect, close to the tip, a third diffuse vascular swelling, soft to the touch.

Laboratory Findings: Routine laboratory examinations (blood morphology, chemistry, stool and urine) were normal. Special endocrinologic examinations

FIG. 2A. Radiogram of left hand.

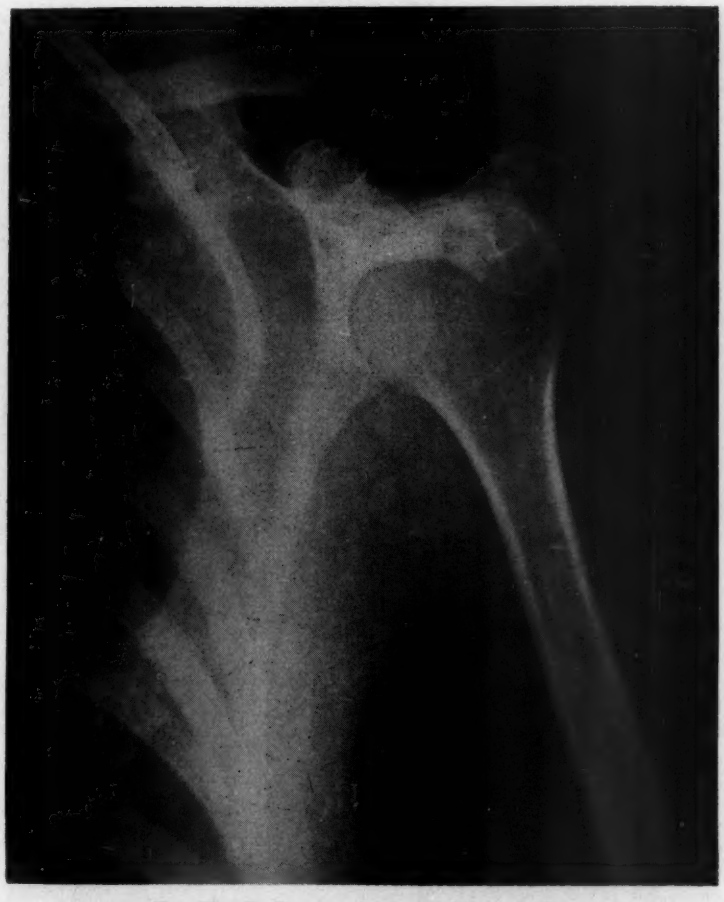

FIG. 2B. Radiogram of left shoulder and ribs.

(follicle-stimulating hormone, ketosteroids, Thorn test, Kepler test, paper chromatography, electrophoresis), as well as an electroencephalogram, electrocardiogram and examination of the fundus oculi, were normal.

Biopsy examinations were performed from three places. A node from the foot showed the typical microscopic structure of a hemangioma, while in a growth from the chest wall the pathologic diagnosis was lymphangioma. A punch biopsy was taken from a recent skin lesion, and the results of this examination will be discussed below.

Radiologic Findings: The radiologic examination showed the following changes in the bones and the soft tissues. Upper limbs: shortening and bending of the ulna and dislocation of the head of the radius on the left side; numerous enchondromata in the metacarpals and phalanges; some phleboliths in the soft tissues (figure 2A); enchondromatous changes in the left scapula and the sixth rib on the left side (figure 2B). Lower limbs: deformity of femur, tibia and fibula on the left side;

typical arrangement of the cartilage masses in the distal metaphysis of the femur; irregular broadening of the soft tissue shadow, with numerous phleboliths; enchondromatous changes in the bones of the right foot (figures 3A and 3B).

These findings were consistent with a diagnosis of Maffucci's syndrome (dys-

FIG. 3A. Radiogram of left leg.

FIG. 3B. Radiogram of left foot.

chondroplasia associated with cavernous hemangiomata and phleboliths in the soft tissues).

Course: The patient was afebrile within four days, after having received penicillin for the breast condition, which was at first considered to be an erysipeloid lesion and which receded quickly, as mentioned above. The subsequent course was uneventful with the exception of a remarkable skin eruption which developed on the left chest wall below the angle of the scapula. The patient complained of a burning feeling in this region, and examination revealed a group of raised, red, elongated patches, each approximately 3 to 5 cm. long and 0.5 cm. wide. There was no associated fever or constitutional upset. Within a matter of days the signs of inflammation receded and bandlike patches of pigmentation appeared that were similar to the previously described pigmentary changes on the thorax and abdomen (figure 4).

The punch biopsy referred to previously, taken from this area of pigmentation, on microscopic examination showed groups of lymph vessels within the papillary layer of the skin, resembling lymphangiectases (figure 5).

A further unusual observation was made during the patient's stay in hospital. On uncovering the left leg we frequently observed beads of sweat on the dorsum of the left foot, limited to an area corresponding to the tortuous veins on the medial aspect. This phenomenon was not observed on other parts of the body. Measurement of the skin temperature of the legs revealed marked differences. The sweating area was 8° F. higher in temperature than the corresponding parts of the right leg, and the toes of the left foot registered 3° F. in excess of the right foot.

The patient, on discharge, was referred for rehabilitation to the appropriate social service.

DISCUSSION

Maffucci's syndrome consists of a combination of the dyschondroplasia of Ollier with multiple hemangiomata. The latter are more obvious in the skin

of subcutaneous tissues and mucous membranes, but it would appear from the few cases that have come to autopsy that they may occur in internal organs as well. The hemangioma is not the only skin lesion, since previous authors have noted, as we have, that there may be associated vascular changes in the form of phlebectasia and lymphangiomata. We may now add lymphangiectasis to this list.

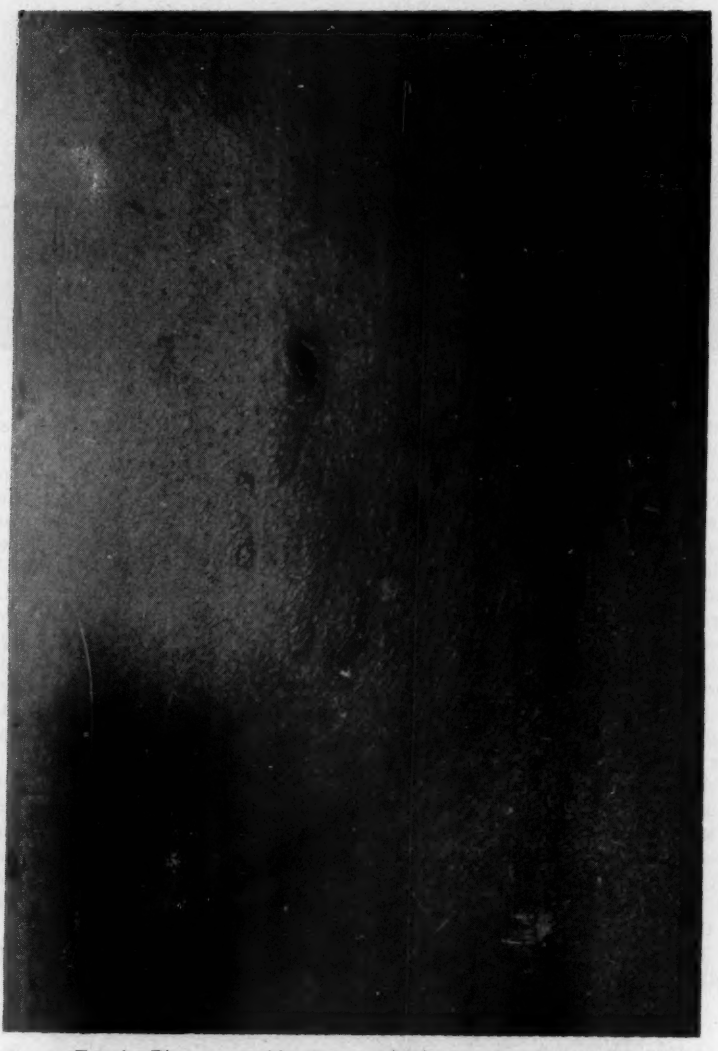

FIG. 4. Pigmentary skin changes of left posterior chest wall. Place of skin biopsy visible.

FIG. 5. Skin biopsy of left posterior chest wall showing lymphangiectasis.

The lesions commence early in life, progress as a rule up to the end of the growth period, and may lead to gross skeletal deformities. There is uneven growth of bone due to defects of ossification with enchondromatous changes, resulting in a tendency to frequent fractures during the period of bone growth. The sequence of the appearance of bone and angiomatous lesions is variable. There is no particular geographic or racial distribution, and inheritance does not appear to play part in its occurrence. Of the 34 previously described cases 18 were males and 13 were females, and in three cases the sex was not indicated.

We do not propose to enter into a discussion of the pathogenesis of the condition. The consensus veers towards the view that the lesions consist of a congenital mesodermic dysplasia, probably due to multiple defects of a single gene. Carleton et al.[1] have discussed the probable connection between the vascular changes and bony lesions, and conclude that they are more likely to be coincidental than consequential.

The pathogenesis of the pigmentary changes (vitiligo, skin discolorations) in the few cases described by Carleton,[1] Bean [2] and Aimes [3] does not appear to have been sufficiently clarified, hence the attempts of Aimes to subclassify the syndrome into the classic Maffucci's syndrome and Kast's syndrome, consisting of dyschondroplasia, hemangiomata and skin discoloration. For this reason he also seeks to relate Maffucci's syndrome with other mesodermal dysplasias with and without bony derangements, e.g., fibrous dysplasia, Klippel-Trenaunay and Sturge-Weber syndrome, as well as the case described by Zellweger et al.[4] of dyschondroplasia with nevus.

There seems to be doubtful justification for this relation, since we believe we have shown in our case that a pigmentation may have its origin in vascular lesions. As noted in the case report, our patient had two phases of inflammatory skin changes (on the breast and on the back), both ending in skin pigmentations similar in every respect to that which we had noted on admission on other parts of the skin. The punch biopsy of the skin from the inflammatory area during subsidence of the inflammation revealed lymphangiectatic changes as the main pathology. We do not know the cause of this inflammatory process, but it should be remembered that the patient had described the occurrence of previous skin "rashes." At the time of admission there was an undoubted inflammation in and over the mass felt in the left breast. It seems more than likely, therefore, that all pigmentations in this entity have their origin in vascular lesions.

The mass in the breast can be regarded as an angiomatous formation, in conformity with similar observations of Bean [2] and Carleton.[1]

Perhaps this unusual activity of the process in the skin and in the deeper tissues at a rather late age may relate to the frequency of malignant changes in the various elements (bony and vascular) reported in Maffucci's syndrome. The survey of the literature brings to light nine certain and three probable malignancies in the total of 34 cases, resulting in an incidence of around 30% malignancy, which is unusually high in an apparently benign condition.

Sweating and temperature changes over a limited hemangiomatous area has only once been mentioned previously.[1] In our case this feature occurred in the area of maximal hemangiomatous change (left foot). A thorough discussion of the possible causes of this localized sweating was presented by Carleton and

associates, but it appears that the genesis of this phenomenon is rather uncertain. Unfortunately, our patient would not submit to further investigations.

We have stressed the special aspect of the pigmentary changes. Our observations in this respect may help to clarify the apparent confusion in the literature regarding the classification of the syndrome into subgroups. This subdividing (depending upon the presence of pigmentation) would appear to be unnecessary if our contention that the pigmentations have their origin in vascular abnormalities is further substantiated.

Summary

1. An additional case of Maffucci's syndrome has been reported, the thirty-fifth case in the literature.

2. Inflammatory lesions of the skin were observed during the course of the disease.

3. A further example of breast tumor, probably hemangiomatous, has been recorded.

4. Localized sweating and temperature changes were observed.

5. Lymphangiectatic spaces in the skin are being added to the list of vascular abnormalities in this syndrome.

6. It is contended that pigmentary changes in Maffucci's syndrome have their origin in vascular lesions.

Summario in Interlingua

Esseva observate un caso de syndrome de Maffucci (dyschondroplasia con hemangiomas multiple), occurrente in un femina de 40 annos de etate. Isto es le trenta-quinte caso reportate in le litteratura.

Esseva trovate multiple deformitates con alterationes enchondromatose del ossos, insimul con lesiones del pelle e del membranas mucose que consisteva de phlebectasias e hemangiomas. Le histos molle contineva numerose phlebolithos. In plus, un distribution erratic de discoloration brunastre del pelle esseva notate, e etiam alterationes inflammatori del pelle que se disveloppava in lesiones pigmentari. In iste lesiones pigmentari, spatios lymphangiectatic esseva trovate per le examine microscopic. Un massa in le mamma sinistre esseva considerate como un formation angiomatose in stato temporari de inflammation. Le inusual activitate inflammatori del processo in le pelle e le histos profunde a un etate plus tosto avantiate pote esser relationate al observate e reportate frequentia de alterationes maligne in le varie elementos ossee e vascular de iste morbo. Le observate alterationes pigmentari, con precedente conditiones inflammatori que presentava un character vascular, rende probabile que le lesiones pigmentari observate in iste entitate ha lor origine in processos vascular. Le classification del syndrome in sub-gruppos, in dependentia del presentia de pigmentationes, esserea alora innecessari. Sudoration localisate e alterationes temporari del temperatura esseva observate in le gamba e pede sinistre al sitos de grossier deformitates vascular.

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MUMPS MYOCARDITIS: CASE REPORT WITH REVIEW OF THE LITERATURE *

By Glenn E. Horton, M.D., *Memphis, Tennessee*

The common acute infectious diseases are usually benign, but occasionally complications may arise from invasion of a vital organ. Awareness of this by the clinician should aid in prompt recognition and therapy. Myocardial involvement is one complication that may arise. A case of probable myocarditis in the presence of mumps posed a problem in differential diagnosis and treatment at this hospital and is discussed.

Mumps (epidemic parotitis) has been recognized as a clinical entity since antiquity, and has subsequently been considered to be an acute systemic disease of specific viral etiology, with a special predilection for the parotid glands. Such complications as orchitis, pancreatitis, oophoritis, mastitis, and meningitis or meningo-encephalitis, have been reported in the past.[1] Myocarditis has until recent years been considered to be a rare and unusual complication of mumps.

Review of the Literature

In 1918 Pujol,[2] a French military surgeon, first surmised that myocardial involvement was a complication in some cases of mumps. He described three cases in French soldiers in whom, because the patients developed dyspnea or substernal pain after or during recovery from mumps, he suspected involvement of the myocardium. Unfortunately, no electrocardiographic studies or other corroborative data were available at that time.

In 1925, on the basis of clinical observation, Barbato [3] suspected mumps myocarditis. In 1932, Manca [4] was the first to report pathologic sections from a case of acute interstitial fibrinous myocarditis occurring in a fatal case of mumps, which prompted him to state: "The mumps virus can attack the heart, and the lesion consists of an acute interstitial myocarditis, especially characterized by a fibrinous exudate which differentiates it from other forms of myocarditis, and may be considered as a peculiarity of this infection."

Stimulated by these observations, in 1944 Wendkos and Noll [5] undertook a random cardiac survey of 15 American soldiers convalescing from mumps.

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They demonstrated electrocardiographic changes in one patient, manifested by sinus bradycardia, T-wave changes, and prolongation of the P-R interval. They further demonstrated temporary shortening of the A-V conduction time following administration of atropine sulfate. This effect was interpreted as evidence that the prolonged P-R interval resulted from increased vagal tone, a response similar to that observed in active rheumatic carditis.[6]

Rosenberg,[7] in January, 1943, observed an instance of complete heart block in an electrocardiogram of a patient convalescing from epidemic parotitis which, in the absence of any other etiologic factor, he considered ascribable to mumps myocarditis. Early in 1944 Rosenberg observed another patient who, during the course of mumps, developed electrocardiographic manifestations of partial heart block which progressed to complete heart block, and ultimately returned to normal. On the basis of these observations Rosenberg [8] undertook a systematic study of the electrocardiographic changes accompanying mumps. Sixteen of 104 patients with epidemic parotitis (15.4%) showed myocardial involvement with a variety of electrocardiographic changes; of the 16, only five had an elevated sedimentation rate, four had leukocytosis, and seven had signs of mumps orchitis. In all but one of these cases the electrocardiographic changes occurred between the fifth and tenth days of the illness, and usually returned to normal in from two to 35 days. Although complete recovery was the rule, a few electrocardiographic abnormalities persisted for from three to five months. Felknor and Pullen [9] in 1944 observed a case of mumps in whom clinical and electrocardiographic changes were compatible with myocarditis.

In 1949 Bland [1] added an additional case to the literature. This case is unique in that the myocarditis with symptoms of left ventricular failure and electrocardiographic changes consisting of decreased QRS amplitude with premature auricular contractions and occasional ventricular escape preceded the fully developed acute parotitis. On the basis of this case, it would seem worthwhile to suggest the use of the complement fixation test [10] and the intradermal test of Enders,[11] using the mumps antigen as diagnostic aids in detection of obscure myocarditis. Bland's patient also had complicating meningo-encephalitis and pancreatitis, as well as the parotitis, suggesting widespread distribution through the blood stream. Bland [1] pointed out that as mumps is frequently not reported, a statistical study is difficult to accomplish, and electrocardiographic study in all infectious diseases might well prove fruitful when feasible.

In addition to this case, Irvin, Bacharach and Pullen [12] in 1951 added another case to the growing literature on mumps myocarditis. Bengtsson and Örndahl [13] reported electrocardiographic changes in 4.4% of 564 cases of mumps admitted to the Stockholm Hospital for Infectious Diseases during 1950 through 1952. They concluded that the occurrence of myocarditis is probably not uncommon in mumps, especially in adults. They also pointed out the high incidence of electrocardiographic changes in the presence of the meningo-encephalitic complication of mumps. The case of probable mumps myocarditis reported in this paper also had signs of serous meningitis.[14]

Case Report

The patient, a 41 year old Negro male cotton tenant farmer, developed right parotid swelling on May 1, 1956, followed by submaxillary and then left parotid

swelling and temperature of 104° F. two days later, when he saw his local physician. The diagnosis of epidemic parotitis, or mumps, was given. While the parotid gland swelling was subsiding the patient developed severe headache, with photophobia and nuchal pain and stiffness. The headache was aggravated by body movement and by the cough which was also present.

Past history revealed possible unilateral mumps without complications in 1931.

Other history revealed prior hospitalization at this hospital in 1954 for maxillary sinusitis, at which time an electrocardiogram (figure 1) was interpreted as borderline; precordial lead U waves were noted, and the question of slight terminal T wave negativity in V_3 and V_4 was raised. It was also noted on the 1954 electrocardiogram

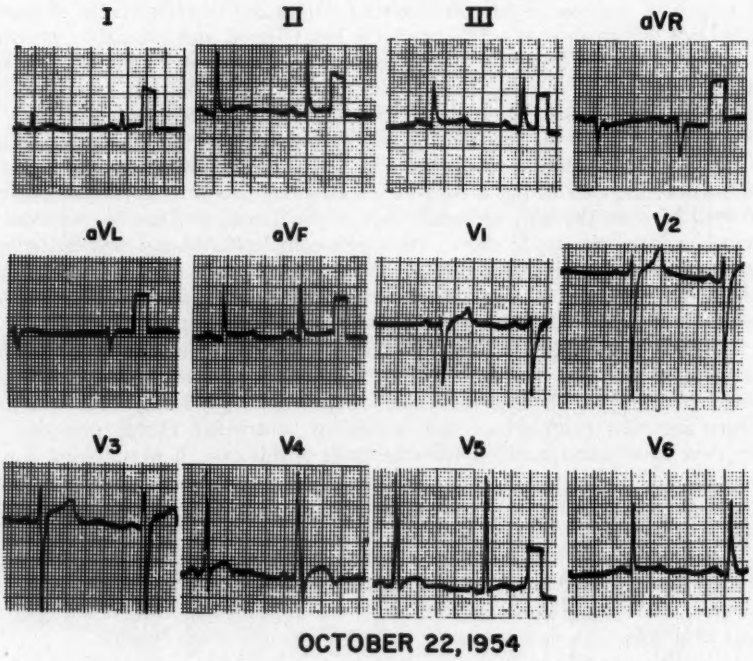

FIG. 1. Electrocardiogram prior to mumps myocarditis.

that the diphasic R-S deflection in aV_L and the tall R wave in aV_F were compatible with a vertically oriented heart; the T wave changes in V_3 and V_4 were subsequently considered positional due to respiratory effect, as similar changes were abolished by the respiratory maneuver of deep inspiration on a subsequent electrocardiogram. His blood pressure in 1954 was 140/100 mm. of Hg, and the chest roentgenogram was interpreted as negative. Family history revealed that his father was hypertensive.

On the basis of complaints referable to mumps, the patient was re-admitted to our hospital on May 13, 1956, with a temperature of 102° F., nuchal rigidity, increased cerebral spinal fluid pressure (normal cell count and protein content), and mild epigastric pain radiating directly to the back. His temperature returned to normal on the evening following admission and he remained afebrile thereafter. Subsequent

serial serum amylase determinations were slightly elevated, but not greatly so. Blood counts were within normal limits. No change from the 1954 chest roentgenogram was noted. The blood pressure was 110/80 mm. of Hg on this re-admission.

Liver function tests were normal during the course of hospitalization. Total serum bilirubin was 0.6 mg.%; cephalin flocculation was 1 plus at both 24 and 48 hours, and thymol turbidity was 1.5 units on May 15, 1956. There was no bromsulfalein dye retention at 45 minutes on the May 17 specimen. Follow-up total serum bilirubin on May 23 was also normal.

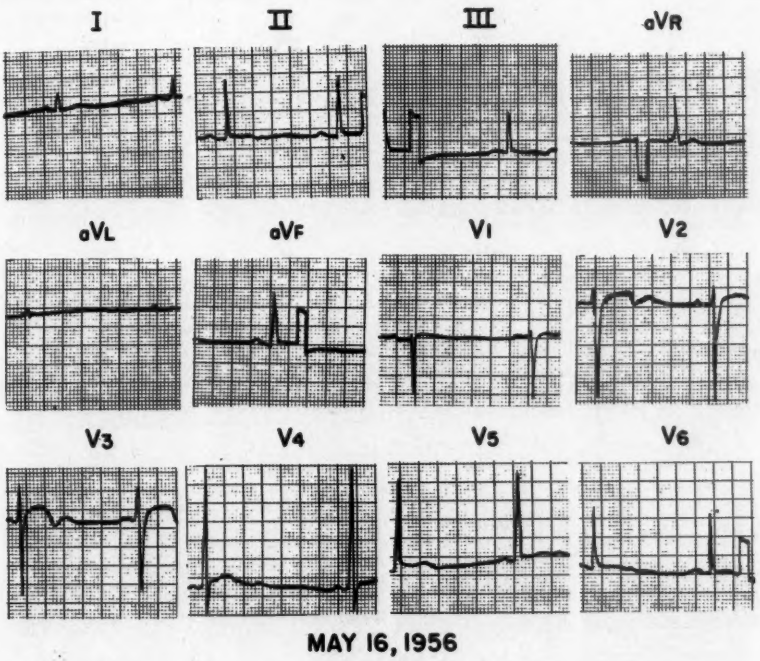

FIG. 2. Electrocardiographic changes during acute mumps myocarditis.

On the evening of the third hospital day, at which time the temperature had returned to normal, the patient developed severe retrosternal pain which lasted two hours and radiated to the left arm over the medial aspect, ulnar distribution, with numbness. An electrocardiogram taken 12 hours later (May 16, figure 2) showed significant change from the 1954 tracing, with sinus bradycardia and ST-T changes. The electrocardiographic diagnosis at this time was felt to lie between acute anteroseptal myocardial infarction, acute mumps myocarditis, and possible respiratory positional effect. A follow-up electrocardiogram on May 23 (figure 3), which also included the left upper chest leads, failed to reveal pathologic changes in the QRS complexes; the reduction in precordial T wave voltage was considered to be due not to the respiratory effect but to another mechanism, such as an acute myocarditis or myocardial infarction.

Following this there was a rapid return toward the 1954 electrocardiographic findings, as indicated on May 28 and on the June 28 tracings (figure 4), which

further ruled against myocardial infarction. The probability of acute coronary insufficiency occurring as a complication of this acute infectious disease of mumps was considered possible but appeared unlikely.

Serum transaminase (SGO-T) determinations were obtained on May 23, with the electrocardiographic changes still present (figure 3). Daily transaminase determinations were then obtained for several days and several times weekly thereafter, including one determination within a two-hour period after another episode (June 7) of retrosternal sensation of oppressive discomfort associated with dyspnea. All serum transaminase determinations were within normal limits. C-reactive protein

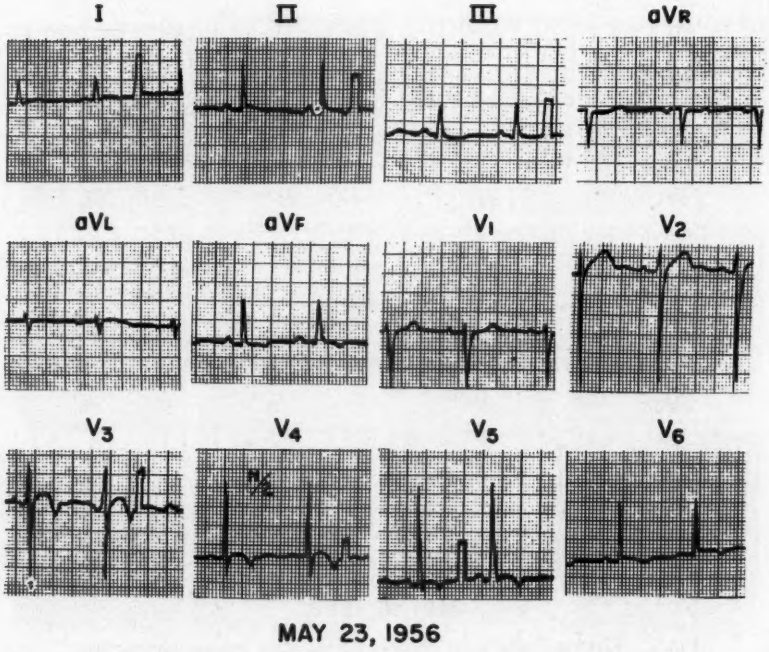

FIG. 3. Further serial electrocardiographic changes during acute mumps myocarditis.

determinations were also within normal limits. The subsequent Master's two-step exercise test of coronary reserve was negative. The total serum cholesterol was 210 mg.%.

During this period of hospitalization there was a fourfold change in the mumps complement fixation titer, varying between levels of 1:64 and 1:512, which is believed to be significant of active mumps infection.

Clinical improvement paralleled electrocardiographic improvement. Following an episode on June 7 of a retrosternal sensation of oppressive discomfort with dyspnea, the patient was asymptomatic. The sedimentation rate, which had previously been elevated and was believed to be associated with active mumps infection, was first found to be normal on July 26. Pulmonary function tests were carried out during the convalescent period with the Collins Respirometer; the values were within the range of normal. The mild improvement after bronchodilator therapy was probably

due to increased efficiency upon repetition of the procedure, rather than to actual bronchodilator effect itself.

After stabilization of the electrocardiogram for at least two weeks the patient was given a 30-day leave of absence. On his return from leave, at which time the previously mentioned normal sedimentation rate was obtained, there was no evidence of relapse of mumps myocarditis. The electrocardiogram at this time was unchanged. Serial electrocardiographic changes are illustrated in figure 5.

Corticosteroid therapy was discussed when the presumed mumps myocarditis was active but was not considered to be indicated in this particular case, as will be discussed subsequently.

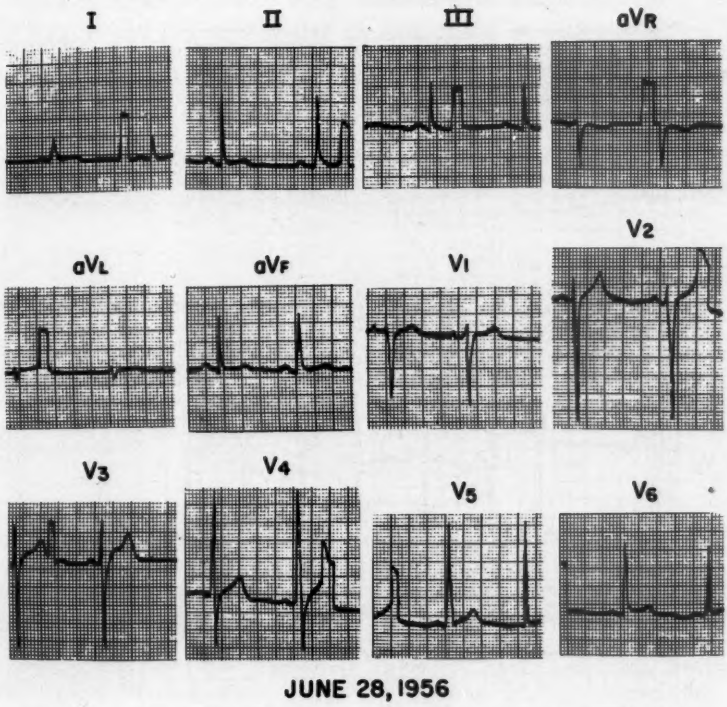

FIG. 4. Electrocardiogram after recovery from mumps myocarditis.

DISCUSSION

What is myocarditis? In the past, many physicians here and abroad designated almost every disease of the heart muscle as "myocarditis." In the majority, the disease was probably replacement fibrosis of the myocardium incident to coronary atherosclerosis, or inadequate coronary blood supply to a myocardium hypertrophied by arterial hypertension.[15]

In time, the pendulum swung to the other extreme. Few clinicians made a diagnosis of myocarditis except in the presence of rheumatic fever, though many of them were aware of the present-day meaning of the term—namely, inflammation of the myocardium.

Renewed interest in clinical recognition of myocarditis was stimulated by the meticulous pathologic studies and review by Saphir,[16] and the innumerable reports of electrocardiographic abnormalities, particularly in the presence of acute infectious diseases, from military and veterans hospitals during and following World War II.

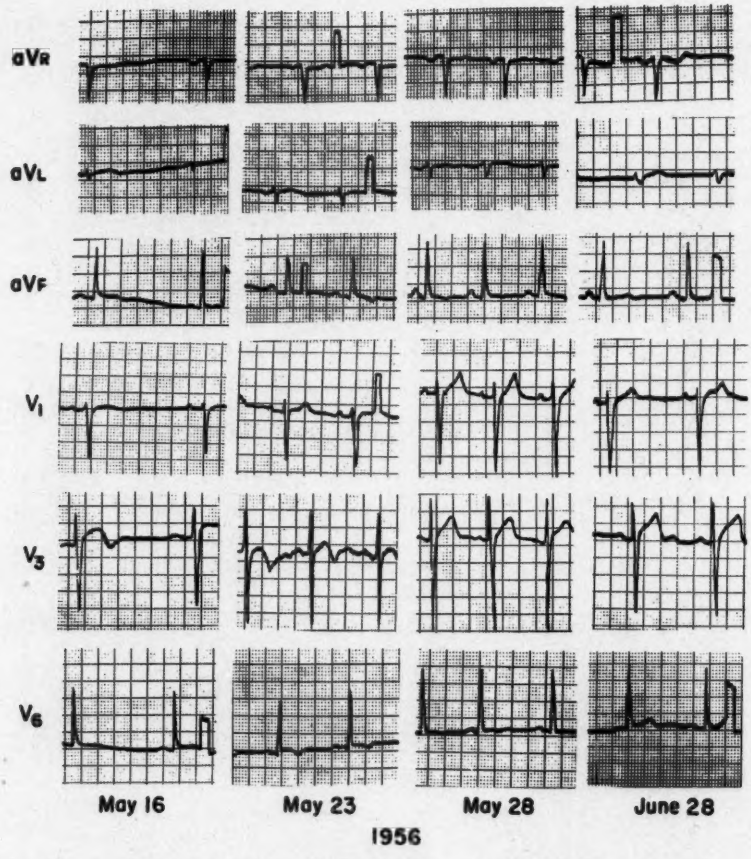

FIG. 5. Composite electrocardiographic changes evolved during a case of acute mumps myocarditis.

Clinically, the signs and symptoms of myocarditis are by no means specific. In fact, they are not infrequently very slight or completely absent. As noted in Rosenberg's 16 cases,[8] only four had clinical evidence of cardiac involvement, and he suggests that a majority of cases of mumps myocarditis follow a subclinical course and require electrocardiographic studies for their recognition. Because of the potentiality of cardiac enlargement and intervening heart failure in acute myocarditis, as well as unexpected sudden death, Chapelle and Koss-

mann [16] point out that the electrocardiogram assumes great importance as the laboratory aid which may first show suspicious evidence of this lesion.

The manifestations of acute myocarditis on the electrocardiogram are variable. The dominant effect is on the labile recovery process represented in the finished record by the S-T segment and the T wave; myocarditis dominantly affects this process. As pointed out by Prinzmetal,[17] in contrast to the stable QRS component of the electrocardiogram, the S-T segment and the T wave are unstable because of their dependency on certain as yet poorly understood dynamic biochemical reactions that take place after the completion of myocardial activation. Thus there is need for careful differentiation and interpretation of the electrocardiogram, in that extracardiac as well as other cardiac mechanisms may produce S-T segment and T wave changes. An example of this was noted in this current case report, where terminal T wave negativity in V_3 and V_4 (figure 6),

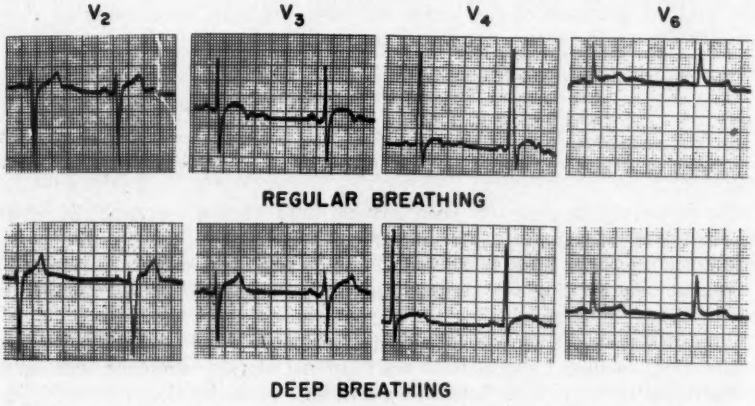

FIG. 6. T wave changes in V_3 and V_4 altered by deep inspiration (July 25, 1956).

before and after recovery from the mumps myocarditis, could be altered in the opposite direction by deep inspiration, which had to be considered in the interpretation of the total electrocardiogram in this case.

Of course, cardiac causes aside from myocarditis, and others also previously mentioned, must be considered in the interpretation of the electrocardiogram. We have observed in our review of the literature that in mumps myocarditis the process may actually affect one or several of the following processes: rhythmicity, conductivity, and the basic processes of excitation and recovery in both the atria and the ventricles. These effects will manifest themselves in the electrocardiogram as abnormal rhythms and premature contractions, atrioventricular block, and modifications in the form, amplitude and duration of the deflections comprising the atrial and ventricular complexes. These changes, single or multiple, can be anticipated in mumps and other myocarditides.[15]

In view of the high incidence of complication of mumps and other infectious diseases in adults,[13, 18] a higher incidence of myocarditis is anticipated, and more frequent serial electrocardiograms when possible have been advocated by several authors.[1, 5, 8, 12, 13, 15, 16, 19] Bengtsson [13] suggests that myocarditis should be

looked for particularly in a case of mumps complicated by meningo-encephalitis.

The serial serum glutamic oxaloacetic transaminase (SGO-T) determinations in this case were within normal limits. Wroblewski and his group [19] reported a 50% increased activity of the SGO-T levels, persisting for as much as three weeks or longer in patients with clinical or histologic evidence of active rheumatic carditis. The significance of the normal level in this case of presumed mumps myocarditis may be indeterminate, since the measurement was made eight days after the onset of the retrosternal pain. However, in view of the previously prolonged SGO-T levels in rheumatic carditis,[19] the normal values here may be significant. Also, one determination was obtained two hours after recurrence of retrosternal pain and was normal.

Petersdorf and Bennett [20] alluded to possible hepatic involvement in nine of 11 cases of mumps where liver function tests showed definite abnormalities. In our case there was no impairment of sulfobromophthalein (bromsulfalein) clearance, and no elevation of the serum bilirubin, cephalin flocculation or thymol turbidity during the active course of mumps infection.

Review of Therapy

If manifestations of myocardial involvement appear—such as congestive failure and arrhythmia—the necessary measures to combat them must be instituted.

Corticosteroid therapy has been advocated in Fiedler's nonspecific myocarditis, and in the rheumatic and the hypersensitivity types of myocarditis.[15] Also, these hormones have been advocated in the management of other complications of mumps, such as that of the orchitis,[20, 21, 22] the postinfectious encephalitis [21] and the acute pancreatitis.[23]

Other infections, such as typhoid fever, brucellosis and tuberculosis, appear to have been managed successfully with adrenal steroid combined with specific antimicrobial therapy, with favorable alterations in the clinical course.[21] However, in cases of viral hepatitis treated with these steroids [21, 24] without specific virucidal therapy, the relapse rate was felt to be increased, although there had been some initial improvement. Consequently, it may be pertinent that in these cases corticosteroid therapy may be questioned in the face of a generalized viral infection for which no specific virucidal agent has been developed. However, it should be noted that the viral hepatitis relapse apparently responds favorably to reinstitution of steroid therapy,[24] and there has been no aggravation or increased spread of mumps viral infection when the orchitis or pancreatitis complications have been treated with corticosteroids.[20, 21, 22, 23] Thus, it is suggested that if the clinician is tempted to use steroid therapy in a patient with mumps myocarditis accompanied by orchitis, pancreatitis or another complication, it may be well to use prednisone or prednisolone (delta-corticosteroids) in view of the diminished likelihood of salt retention in the presence of potential congestive heart failure.

In the vast majority of cases, the course of the myocarditis complicating the benign acute infectious diseases is uneventful, with recovery on simple bed-rest therapy. Rosenberg [8] advocates a régime of periodic rest, and decreased activity for two to three weeks after the electrocardiogram has become normal. As pointed out by Chapelle and Kossmann,[15] and applied here, "It would seem the

part of wisdom to give all patients with myocarditis occurring in various infectious diseases sufficient rest in bed to permit the myocardial process to pass into a healed stage as determined clinically and electrocardiographically."

Summary and Conclusions

1. A case of probable mumps myocarditis is presented and the pertinent clinical and laboratory findings are discussed. The possibility of acute coronary insufficiency occurring as a complication of an acute infectious disease is admitted, but considered to be less likely.

2. The use of the electrocardiogram in cases of mumps in various stages of the disease is suggested to establish the incidence of cardiac complications, and hence the optimal period for complete convalescence.

3. Experience in the past indicates that functional recovery from myocardial involvement in mumps is usually complete. One death is reported in the literature.

4. Since mumps myocarditis can precede the parotid gland inflammation, the use of the mumps complement fixation and intradermal tests is suggested as diagnostic aids in obscure myocarditis.

5. Serial SGO-T (serum transaminase) determinations in this case were within normal limits, which is probably compatible with the superficial interstitial involvement of the myocardium described pathologically in a previously reported autopsied case of mumps myocarditis.

6. There were no associated abnormalities in liver function tests in this case, although attention has recently been focused upon the possibility of hepatic involvement in mumps.

7. Corticosteroid therapy has been advocated in other types of myocarditis, but it is probably not indicated in uncomplicated mumps myocarditis, which usually does very well on convalescent bed-rest therapy alone. However, in the presence of additional factors, such as mumps orchitis, pancreatitis or other complications, delta-corticosteroid (prednisone or prednisolone) therapy may be considered.

Acknowledgment

Appreciation is expressed to Dr. Charles V. Dowling and Dr. Frederick H. Knox, Jr., of the Medical Service, for their review of the data, and to Mr. Alex Gravesen and Mr. Herbert Schonert, of the Medical Illustration Laboratory, for their assistance.

Summario in Interlingua

Jam le ancianos cognosceva le entitate clinic que es designate per le termino parotiditis epidemic e habeva recognoscite su predilection special pro le glandulas parotidee. Complicationes como orchitis, pancreatitis, oophoritis, mastitis, e meningitis o meningo-encephalitis (o le duo) ha essite reportate in le passato. Usque recentemente, myocarditis esseva considerate como un rar e inusual complication de parotiditis. Es presentate un caso probabile de myocarditis in parotiditis occurrente in un masculo negre de 41 annos de etate. Le pertinente constatationes clinic e laboratorial es discutite. Es presentate electrocardiogrammas serial que illustra le evolution del segmento S-T e alterationes del unda T. Le possibilitate que acute insufficientia coronari occurre como complication de acute morbo infectiose es admittite, sed in le presente caso un tal explication es considerate como pauco probabile. Le patiente se restabliva sin incidente, per un simple therapia de allecta-

mento e reposo. Le uso de un therapia a corticosteroide esseva prendite in consideration, sed illo non esseva considerate como indicate in iste caso de non-complicate myocarditis in parotiditis. Determinationes serial de transaminase glutamic-oxaloacetic in le sero se teneva, in le presente caso, intra le limites normal. Isto es probabilemente compatibile con le presentia de un affection interstitial al superficie del myocardio que ha essite describite pathologicamente in le passato in le reporto necroptic de un caso de myocarditis in parotiditis.

Es presentate un revista del litteratura concernite con le presente thema. Isto es sequite per commentos de interesse therapeutic. Es suggerite le uso del technica electrocardiographic in casos de parotiditis a varie stadios, con le objectivo de establir le incidentia de complicationes cardiac e assi le periodo optimal pro un convalescentia perfecte. Experientias in le passato indica que le restablimento functional ab affectiones myocardial in casos de parotiditis es usualmente complete. Un caso mortal es reportate in le litteratura. Le uso de therapia a corticosteroide pote esser prendite in consideration in le presentia de factores additional, i.e. per exemplo de orchitis, de pancreatitis, o de altere complicationes de parotiditis.

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CHICKENPOX PNEUMONIA TREATED WITH PREDNISOLONE: A CASE REPORT *

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THE benign viral diseases of childhood occasionally appear in adult life with serious and even fatal consequences. Severe widespread pneumonitis is one of the rare complications of varicella. The pulmonary inflammatory disease is thought to be a direct result of invasion by the chickenpox virus.

Until 1956 only 15 cases of chickenpox pneumonia had been reported in the literature.[1-15] Since that time 36 additional cases have been described, bringing the total number to 51.[16-22] Treatment of these patients has consisted mainly of general supportive measures, along with various antibiotics. Two case reports describe the use of cortisone and hydrocortisone in seriously ill patients.[11-19]

This case is reported to reëmphasize the severity of varicella pneumonia and to report what we consider a favorable therapeutic response to prednisolone. In addition, the recent literature will be briefly reviewed.

CASE REPORT

A 31 year old white housewife was admitted to the hospital on March 17, 1957, complaining of cough, fever, blood-tinged sputum and vesiculopustular skin lesions. One of her children had had chickenpox two weeks previously, and another developed a rash coincident with the onset of the patient's illness.

The past history was noncontributory.

Four days prior to admission the patient had noted development of scattered vesicular lesions on her face, trunk and extremities. This was soon followed by chills, fever and cough, which rapidly progressed in severity. During the ensuing three days the cutaneous lesions spread to involve the entire body. The cough became productive, and the temperature rose to levels of 103 to 104° F. daily. By the morn-

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ing of admission to the hospital there was a large amount of blood tinged sputum, and dyspnea was marked.

Physical examination at the time of admission revealed an acutely and seriously ill young female. The respirations were rapid and labored, with a rate of 36 per minute. The lips, mucous membranes and nail-beds were cyanotic. The patient coughed frequently, raising large amounts of thin, frothy, pink-tinged sputum. The

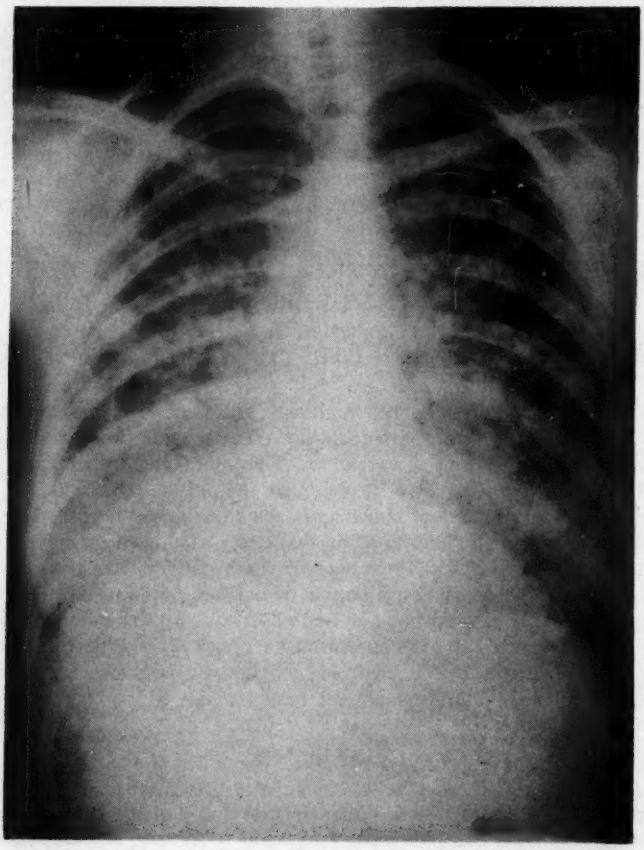

FIG. 1. Admission chest film, taken March 17, 1957, showing widespread bilateral nodular infiltration.

skin was covered with the characteristic vesiculopustular lesions of chickenpox in all states of development. In addition, a few lesions were present on the buccal mucous membranes. The pulse rate was 120 per minute, and the blood pressure, 110/60 mm. of Hg. The temperature was 99.4° F. Examination of the lungs revealed no dullness and only a few medium moist râles in the left lung base. The heart was not enlarged, and no adventitious sounds were detected. The remainder of the physical examination was not remarkable.

Laboratory tests revealed a white blood count of 8,000, with a normal differential.

The hemoglobin was 15 gm. The urinalysis was within normal limits except for 1 plus albuminuria. The serologic test for syphilis was negative. Serial cold agglutination tests and a Q fever complement fixation test were negative. Skin tests for tuberculosis and histoplasmosis were both negative. Smears and cultures of the sputum revealed the usual bacterial flora, and in particular were negative for acid-

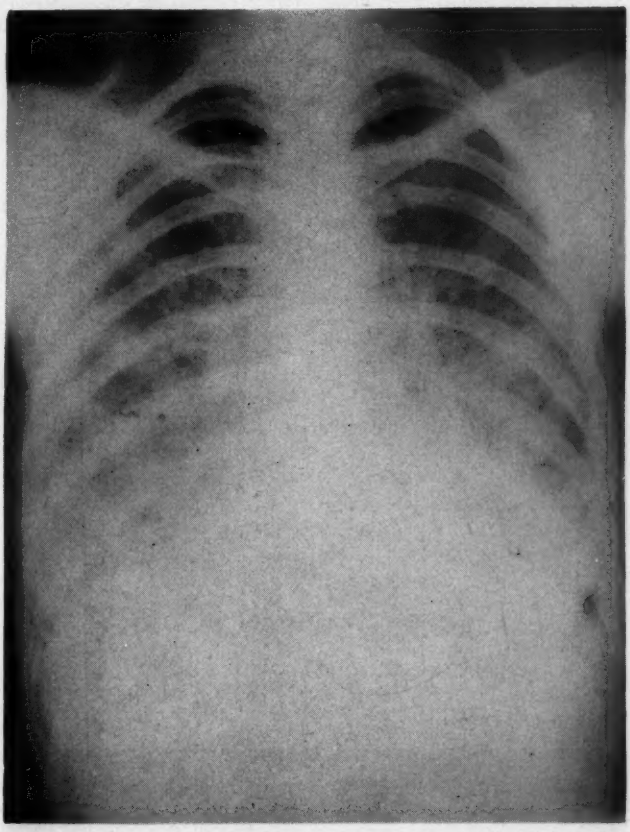

FIG. 2. Chest film made March 23, 1957, showing minimal clearing in upper one third of each lung field.

fast bacilli and fungi. An x-ray of the chest at the time of admission (figure 1) showed widespread bilateral nodular pulmonary infiltrates. Serial x-rays made during the hospital stay are seen in figures 2, 3 and 4.

Hospital Course: The admission diagnosis was chickenpox pneumonia. Initial therapy consisted of oxygen with nebulized Alevaire, mild sedation and tetracycline, 250 mg. every six hours. During the first 48 hours the temperature ranged between 101 and 104° F. The sputum became even more copious in amount and frankly bloody. By the end of the third day the sputum was thick and tenacious. Moist râles had become audible throughout both lung fields. The patient was still cyanotic, with rapid, labored respirations, tachycardia and intermittent anterior chest pain. At

this juncture prednisolone was started in a dosage of 40 mg. per day, divided and given at six-hour intervals. The dose was gradually tapered during the ensuing two-week period. Within 24 hours the temperature had fallen from 103° F. to normal levels. The patient became much less dyspneic, and in general appeared to be greatly improved. The sputum became rusty in color and rapidly decreased in amount. No new skin lesions were noted after prednisolone was started, and those present rapidly regressed. As expected, appetite and mental attitude greatly improved

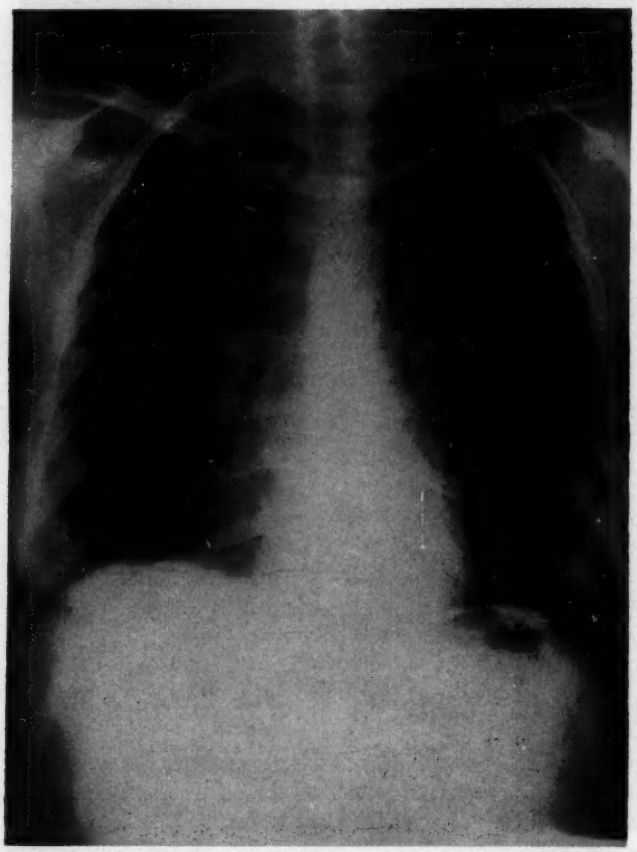

FIG. 3. Chest film made March 29, 1957, showing marked clearing in all but lower third of lung fields.

during the early phase of steroid therapy, and at no time were there adverse side-effects from treatment. X-ray three weeks following admission revealed almost complete resolution of the pneumonic process.

DISCUSSION

The various clinical manifestations and laboratory findings in varicella pneumonia have been adequately summarized in a recent report by Weinstein and

Meade.[18] Most of the cases, including our own, have followed a fairly uniform pattern, consisting of development of fever, chickenpox rash, severe cough, dyspnea and large amounts of sputum. Hemoptysis occurs not infrequently, and anterior chest pain is occasionally noted. Characteristically, as the rash recedes pulmonary symptoms improve, along with the general condition of the patient.

FIG. 4. Chest film made April 6, 1957, showing only very slight infiltration in each base.

The seriousness of this particular manifestation of varicella cannot be overemphasized. There were four deaths among the 15 cases reported up to 1956.[2, 6, 8, 9] Since then there have been four additional fatalities, bringing the total to eight out of 51 cases, or a mortality rate of 16%.[17, 19] The three fatalities described by Fitz and Meiklejohn [19] point up the fulminant nature of this illness. Two of their patients died on the first day and one on the third day. The early signs and symptoms were no different from those enjoying a more favorable outcome.

The pathologic changes usually consist of an exudate of large mononuclear cells and proliferation of alveolar septal cells. There is occasional hyaline membrane formation in the alveoli and areas of necrosis occur involving alveolar cells and surrounding arteries. Polymorphonuclear cells and bacteria are scarce. The type A intranuclear inclusion bodies characteristic of chickenpox may be found. Other organs that tend to be involved include the gastrointestinal tract, liver, spleen, pancreas and kidneys.

The x-ray findings have been described in detail by Tan, Kaufman and Levene.[23] Usually there is a widespread, bilateral nodular infiltration which is usually densest at the bases. In some cases transitory changes are common, with areas resolving and others appearing. The lung roots are increased in prominence, and occasionally a small amount of pleural effusion is seen.

Treatment has consisted largely of general supportive measures and antibiotics. The latter have been used primarily as prophylaxis against secondary bacterial invaders, and there has been no evidence that chemotherapy in any way alters or affects the basic disease process. In reviewing the literature, we have been able to find two cases where cortisone was used in treatment of varicella pneumonia.[11, 19] Rosecan and his group [11] used large doses of cortisone in an extremely ill patient with persistent shock. The drug was discontinued after three days because of the development of congestive heart failure. Little or no improvement was noted in this particular instance. Fitz and Meiklejohn [19] described the use of hydrocortisone and cortisone in a critically ill pregnant female. Apparently there was decided improvement within 24 hours. As in our case, there were no adverse effects from the steroid therapy, and no tendency to post-treatment recrudescence, as has been noted in certain other viral infections.

Steroid therapy in our patient was not decided upon without considerable hesitancy and circumspection. She was treated supportively and watched closely for almost 72 hours before the decision was reached. In view of the lack of favorable progress during this period of observation, the high mortality in previously reported cases, and the general gravity of the situation, prednisolone therapy was instituted. Certainly no definite conclusions can be reached from these two patients as to the efficacy of steroids in varicella pneumonia. However, it does seem likely that this form of therapy did at least support this and the previously reported patient through a critical phase of the illness.

The role of steroids in viral diseases is still uncertain. Excellent results have been reported in the treatment of severe mumps infections.[24] Some are advocating hormones in fulminant viral hepatitis.[25] However, in this particular disease there seems to be a high incidence of post-treatment relapse or recrudescence. Cortisone may shorten the acute phase, lessen the pain and reduce the complications of herpes zoster.[26] The herpes virus on occasion has been linked with the etiologic agent of chickenpox.[27] Further therapeutic trials with steroids seem warranted in certain viral diseases, including severe varicella pneumonia.

Summary

A case of severe chickenpox pneumonia is reported. Therapy with prednisolone was instituted after lack of response to supportive measures and when the patient was desperately ill. Within 24 hours there was marked improve-

ment, and convalescence progressed uneventfully. Steroids seemed to have a decidedly favorable influence on the disease in this instance.

A brief summary of the recent literature has been given.

Summario in Interlingua

Un feminina de racia blanc de 31 annos de etate con sever pneumonia como complication de varicella exhibiva le typic lesiones del morbo primari, esseva satis toxic, e habeva sever embarasso respiratori. Le roentgenogramma del thorace revelava un extense presentia bilateral de nodular infiltratos pulmonar. Antibioticos, oxygeno, sedation, e mesuras supportative general esseva administrate durante le prime duo dies del hospitalisation. In despecto de iste regime, le stato del patiente se aggravava, e illa esseva criticamente malade. Prednisolona esseva instituite, initialmente in doses amontante a 40 mg per die. Intra 24 horas un melioration frappante esseva notate, con defervescentia e subsidentia del dyspnea. Le doses de prednisolona esseva reducite gradualmente, e le melioration continuava sin incidente.

Nos opina que iste therapia supportava le patiente a transverso un phase multo critic del maladia. Un revista del litteratura revela duo altere casos de pneumonia a varicella que esseva tractate con hormones steroide. In un del duo casos, definite beneficios therapeutic esseva effectuate.

Es sublineate le gravitate de iste complication de varicella. Le mortalitate usque al tempore presente ha essite 16%. Ab le puncto de vista pathologic le morbo es characterisate per proliferation de cellulus septal alveolar e exsudation de grande cellulas mononucleari. Altere organos in varie partes del corpore pote esser afficite. Le roentgenogramma revela usualmente extense infiltration nodular bilateral que es le plus dense al bases.

Therapia a steroide ha essite efficace in altere morbos virusal, per exemplo in orchitis post parotiditis e in fulminante hepatitis virusal. Le autores suggere que iste forma de tractamento exerce possibilemente un multo favorabile influentia in pneumonia de varicella.

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MASSIVE NECROSIS OF THE LIVER FOLLOWING IPRONIAZID *

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THE hydrazine derivatives of isonicotinic acid (isoniazid and iproniazid) have been used effectively in the treatment of human tuberculosis. However, significant side-effects have occurred in patients under treatment with these compounds, particularly with iproniazid.[1-4] These included euphoria, nervousness, restlessness, involuntary muscle twitching, hyperreflexia and mild clonus, peripheral neuritis, headache and vertigo. Occasionally, progressive hemolytic anemia and orthostatic hypotension with syncope have been reported from the use of iproniazid.[5]

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From the Samuel S. Fels Research Institute, Temple University Medical Center, Philadelphia, Pennsylvania.
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Iproniazid phosphate, 1-isonicotinyl-2-isopropyl-hydrazine phosphate, has recently been suggested as a "psychic energizer," to restore a feeling of well-being, to promote increase in appetite, weight and vitality, and for use in patients with depression.[6, 7] This compound is a potent inhibitor of mono-amine oxidase,[8] and causes an accumulation of serotonin in brain tissue.[9] While jaundice as a possible complication from the use of this drug is mentioned in the brochure describing the use of the drug for the physician, it is not emphasized as a serious complication in the medical literature. The following report of a patient who developed acute massive necrosis of the liver following the use of iproniazid (Marsilid) is therefore of interest.

Case Report

A 49 year old white female was jaundiced and in deep coma when admitted to Temple University Medical Center. The history was obtained from her husband and her physician. She had been mentally depressed for the preceding four months and had received four electric shock treatments during that period. For the last six weeks she had been placed on iproniazid, in a dose of 50 mg. three times daily. She developed increasing progressive jaundice for one week and had become comatose two days prior to this admission.

Her past medical history was not significant. There was no history of chronic alcohol consumption or blood transfusion, or of her having been in contact with an icteric person.

The patient was critically ill on admission, with marked jaundice and in deep coma. Her blood pressure was 154/88 mm. Hg; temperature, 97.4° F.; pulse rate, 110/minute; respiration, 16/minute. She was a well developed, well nourished female. There was no rash nor petechiae. The lungs were clear. The heart was not enlarged and there was normal sinus rhythm. The abdomen was moderately distended, with a questionable presence of ascites. The liver and spleen were not palpable, and there were no palpable masses. Reflexes in the lower extremities were decreased.

Laboratory Data: The white blood cell count was 12,900; hemoglobin, 14.8 gm.; hematocrit, 45%. The serum sodium was 143 mEq./L.; potassium, 3.5 mEq./L.; chloride, 107 mEq./L.; CO_2 content, 64 vol. %. Her urine was dark brown, turbid, and neutral in reaction, showing a 2 plus albumin, and microscopically, numerous epithelial cells, leukocytes and red blood cells. Serum total protein was 5.7 gm. %, with albumin, 3.6 gm. %, and globulin, 2.6 gm. %. The blood urea nitrogen was 13 mg. %. The liver function tests were as follows: total serum bilirubin, 40.0 mg. %; one minute bilirubin, 16.2 mg. %, and delayed direct, 8.2 mg. %; cephalin cholesterol flocculation, 4 plus; thymol turbidity, 4.5 units, with 18-hour turbidity ratio, 78%. The serum gamma-globulin turbidity was 7.5 units; alkaline phosphatase, 6.9 S. J. R. units; total cholesterol, 99 mg. %, with ester ratio of 16%. The serum glutamic oxalacetic transaminase was 307.2 units, and serum glutamic pyruvic transaminase, 335.6 units. Serum phospholipids were 126 mg. %; total fatty acid, 158 mg. %; neutral fat, 66 mg. %; total lipids, 302 mg. %. Her prothrombin time was 46 seconds "corrected," compared with 10 seconds in the control. The electrocardiogram revealed nonspecific changes in the ST segment and T wave, compatible with those observed in hypopotassemia.

During her hospital stay the patient remained in deep coma. She was treated with an intragastric drip of 20% glucose, potassium, hydrocortisone, Terramycin, nasal oxygen and sodium glutamate. Her urinary output was adequate on the first three days but decreased markedly on the day of her death. Her temperature rose

to 101.2° F. on the second day and remained elevated. She developed Cheyne-Stokes respiration on the morning of her fifth hospital day, and died the same afternoon.

Autopsy Findings: Only the pertinent autopsy findings are included. The skin and sclerae were intensely icteric. The pleural cavities contained approximately

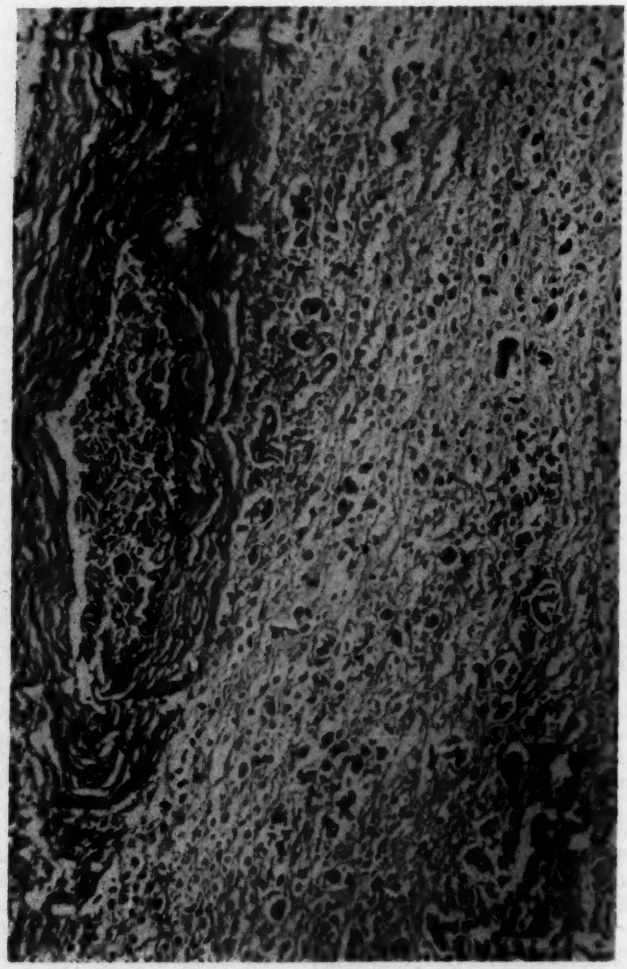

FIG. 1. Low power photomicrograph of the thickened bile duct plugged with desquamated mucosa. Beneath this area there is complete necrosis of hepatic parenchyma (× 100).

350 ml. of clear yellow fluid. There were marked passive congestion and evidence of bronchopneumonia. The heart was grossly normal. The peritoneal cavity contained about 500 ml. of clear yellow fluid. The serous surfaces were smooth and glistening. The liver was normal in shape, yellow-green in color and markedly reduced in size. It weighed 850 gm., and the capsule was uniformly smooth and

thin. The organ was remarkably soft and could virtually be folded completely on itself. The cut surface revealed an obscure liver pattern with a mottling of yellow and grey areas. Histologic section showed massive necrosis of the liver cells (figures 1 and 2). The broad tracts of liver cells in each lobule were absent, with but little granular debris in the collapsed reticular stroma. A few isolated clusters of deeply hyperchromatic liver cells remained about the portal areas. Numerous polymorphonuclear cells, lymphocytes and monocytes, and an apparent increase in bile ducts,

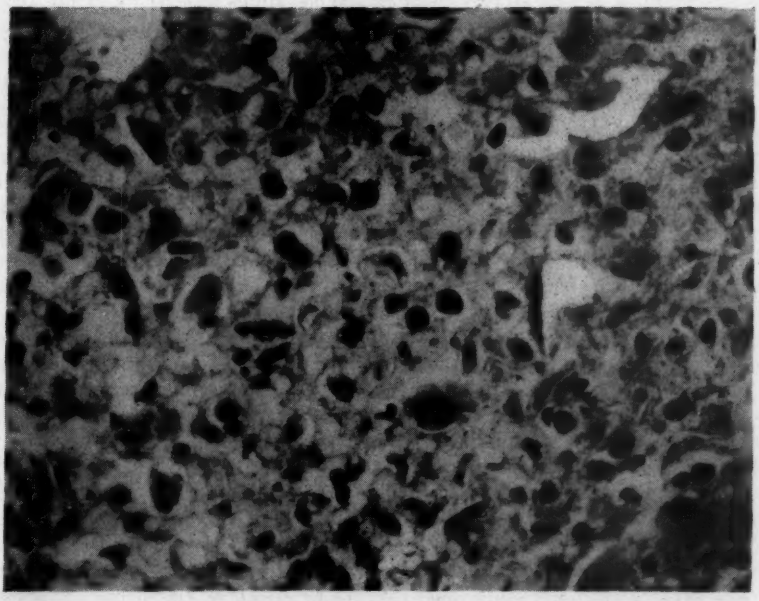

FIG. 2. High power of section of field shows complete necrosis of hepatic parenchyma, with lymphocytes scattered throughout (× 400).

were seen in these areas. There were also areas of recent hemorrhage into the necrotic parenchyma. The esophagus, stomach wall and large intestine were essentially normal, while the kidneys revealed the changes characteristic of cholemic nephrosis.

DISCUSSION

This case is reported primarily to emphasize certain aspects of the jaundice which may complicate administration of iproniazid (Marsilid), and to contrast its character with that induced by chlorpromazine.

Since this patient gave no history of having received a blood transfusion or of having been in contact with an icteric person or of having received any medication except iproniazid for a period prior to the development of her jaundice, one may assume that the jaundice was probably caused by this drug. Iproniazid administration as a cause of jaundice can be implicated only by inference, since the alterations in liver function and the histologic changes found in the liver in

Marsilid jaundice resemble very closely those seen in viral hepatitis. In this patient, first examined apparently in the stage of widespread liver necrosis, and especially in other recovered cases that are being studied for possible delayed effects of the jaundice and will be detailed later,[10] our routine liver function profile has indicated the presence of acute, diffuse hepatocellular disease. These indications, in addition to the hyperbilirubinemia, are positive flocculation tests (cephalin-cholesterol flocculation, thymol turbidity, 18-hour turbidity ratio and gamma globulin), as well as very considerable elevations in serum glutamic oxalacetic and glutamic pyruvic transaminase; serum alkaline phosphatase is elevated only slightly or not at all, as is total cholesterol which, in severe cases, as in similar instances of viral hepatitis, may be below normal. The highest values for transaminase which we have thus far observed in patients in whom Marsilid might be reasonably suspected to be the cause of the jaundice have been 357 units for SGOT and 514 units for SGPT (colorimetric method).[11] Interestingly enough, the higher values for SGPT over those of SGOT again parallel the relationship of these values very often found in viral hepatitis. Significantly too, gamma globulin flocculation was normal in two of three of our cases, and only slightly elevated (10.1 units) in the third. These results contrast sharply with those produced by chlorpromazine jaundice, in which the usual liver function profile consists of normal flocculation tests with significant elevations in phosphatase and cholesterol, in addition to that of the transaminases. Previous studies [12] yielded data on chlorpromazine sensitization that could lead to jaundice, in which we demonstrated that the sensitizing process could be detected and readily reversed by discontinuing the drug. Elevation in serum alkaline phosphatase and of both transaminases before any change in serum bilirubin occurred could be detected readily. From our own experience with iproniazid, the problem with this drug appears to be quite different, and one wonders if a warning period with any test will be available. From our own limited experience with Marsilid hepatotoxicity, we think that serum glutamic oxalacetic and/or glutamic pyruvic transaminase might—if any test would—offer the earliest evidence for developing liver toxicity produced by this drug. However, this can be determined only by frequently repeated liver function studies during the course of Marsilid administration.

Considering the high mortality rate (20% in over 100 cases [13]) of jaundice from the use of this drug, one wonders whether the warning is adequate in the brochures that carry the indications for its use to the physician: "Jaundice has been reported to occur during the administration of Marsilid. It is therefore advisable to watch for this complication and to discontinue the use of the drug at the first indication of jaundice or impaired liver function." We do not know at this time whether progressive acute destruction of liver cells could always be reversed by stopping the drug once liver toxicity has become manifest. As indicated earlier, the close resemblance of changes accompanying the jaundice produced by this drug and those of viral hepatitis complicates very seriously the problem of identifying with certainty jaundice due to this drug.

The liver in our patient was remarkably soft and flabby, and the massive necrosis of the liver cells on histologic examination indicated the severity of the damage produced. DeVerteuil and Lehmann [6] studied 31 patients with depression on iproniazid therapy and reported one death from acute toxic necrosis of the liver following the use of this drug. Details were not given in their

report, but they stressed the fact that this patient had received the smaller dosage schedule of 100 mg. daily, and that the dosage had been reduced to 50 mg. daily 14 days before the onset of jaundice. The patient died 12 days after the onset of jaundice, and acute necrosis of the liver was found at autopsy.

Nothing is known at present regarding a possible mechanism through which iproniazid may produce liver damage. Popper [14] suggests that the liver damage following the administration of this drug may result from the activation by the drug of a latent hepatitis virus in the patient. While one cannot deny such a possibility, it is difficult to understand why a virus that has been dormant in the patient, when activated by the administration of iproniazid, should suddenly acquire such virulence as to cause death in 20% of those afflicted, since latency itself implies a certain degree of immunity in the host.

Summary

The relative lack of emphasis in the literature upon jaundice, and especially upon possibly the fatal outcome of such jaundice from the administration of iproniazid (Marsilid), is indicated.

A patient is described in whom jaundice occurred during the administration of this drug and whose illness ended in death, with the finding of acute liver necrosis. Liver function profile and liver changes in Marsilid jaundice very closely resemble those seen in viral hepatitis and differ strikingly from those encountered in chlorpromazine jaundice.

Acknowledgment

We are indebted to Dr. Herbert Freed for referring this patient.

Summario in Interlingua

Phosphato de iproniazido (Marsilid) ha recentemente essite proponite como "stimulante del energia psychic," capace a restaurar un sensation de ben-esser, a promover le augmentation del appetito, peso, e vitalitate, e a beneficiar patientes in stato de depression. Es describite un patiente in qui jalnessa occurreva durante le administration de iste droga e in qui il esseva constatate al necropsia que ille habeva habite acute necrosis del hepate. Le patiente—un femina de racia blanc de 49 annos de etate—esseva icteric e profundemente comatose quando illa esseva admittite al Centro Medical del Universitate Temple. Durante le precedente quatro menses illa habeva essite mentalmente deprimite, e durante le passate sex septimanas illa habeva recipite iproniazido in un dosage de 50 mg, tres vices per die. Illa disveloppava crescente grados de jalnessa progressive durante un septimana. Illa habeva devenite comatose duo dies ante su hospitalisation. Tests del function hepatic revelava hyperbilirubinemia, positive tests de flocculation (flocculation a cephalina-cholesterol, turbiditate a thymol e proportion de turbiditate post 18 horas), e etiam elevate nivellos seral de transaminase glutamic-oxaloacetic e glutamic-pyruvic. In despecto de un therapia vigorose, le patiente remaneva in coma e moriva le quinte die de su hospitalisation. Le necropsia revelava que le hepate esseva remarcabilemente reducite in su dimensiones e que illo esseva remarcabilemente molle. Le dissection histologic revelava necrosis massive del cellulas hepatic. Le profilo del function hepatic e le alterationes hepatic in jalnessa a Marsilid es similissime a illos vidite in hepatitis virusal e differe frappantemente ab illos vidite in jalnessa per chlorpromazina.

Es signalate le gravitate del prognose in jalnessa post therapia a iproniazido.

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PRIMARY PULMONARY ARTERIOSCLEROSIS WITH RUPTURE OF THE PULMONARY ARTERY *

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Pulmonary arteriosclerosis may be primary or secondary as defined by Ulrich.[1] In a recent textbook of medicine,[2] under the title of "Pulmonary Arteriosclerosis," it is noted that "pulmonary arteriosclerosis and hypertension are dependent upon each other but there is a controversy as to which is cause and which is effect." Rupture of the pulmonary artery without obvious pulmonary disease or heart disease of the type imposing resistance to the pulmonary circulation is rather rare, and for this reason the following case is presented.

* Received for publication September 17, 1957.
From the Davis Memorial Hospital, Elkins, West Virginia.
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Case Report

A 61 year old white married businessman was admitted to the Davis Memorial Hospital on October 27, 1956. His past history revealed no serious illnesses, no operations and no injuries. He had been observed and treated in this hospital in April, 1948, by one of us (R. J. C.) because of spontaneous pneumothorax involving a small area of the left lower lung field. He recovered completely after a few days and remained quite well during the remainder of 1948. At the time of the observation in 1948 the patient had had a normal blood count, his heart size was normal, and serial electrocardiograms were normal. The patient had been examined on three occasions between 1948 and his present illness and no abnormality had been noted.

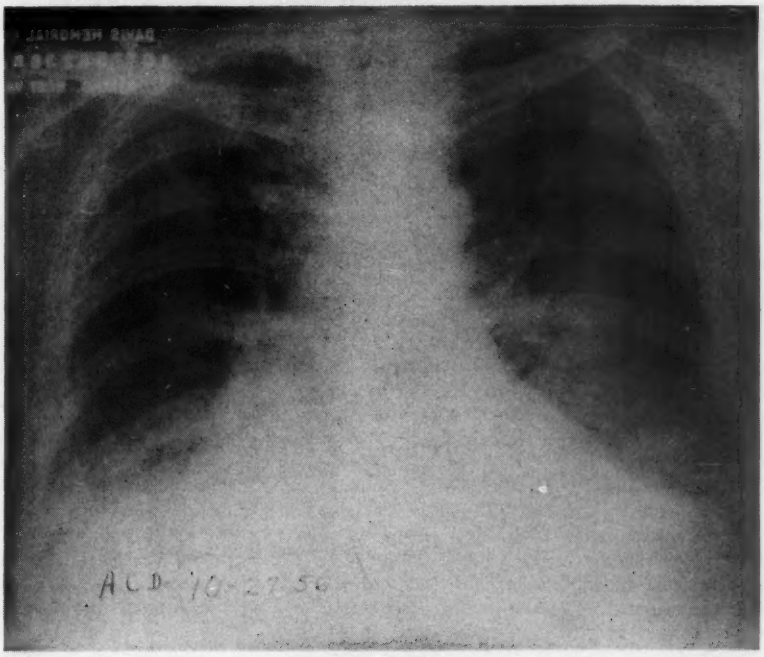

Fig. 1. X-ray of the chest.

The present illness had begun about eight days before admission. He first noted a dry cough, general malaise and dyspnea, which he considered to be a "chest cold." During the next six days the dyspnea became much worse, the cough was productive of occasional blood-tinged sputum, and he was seen at his home by one of us (L. H. N.). Examination at this time disclosed "a normal temperature, a few dry râles were heard at both lung bases, the heart was normal and the blood pressure was 130/80 and the patient did not appear very ill." Because of the prevalence of a mild epidemic of respiratory infections in the community at the time, this was considered to be a respiratory infection. The patient was given an antibiotic and remained home at rest during the next two days, at the end of which he was no better. He had no fever, but the cough and dyspnea were worse and now he also noted orthopnea. On one occasion a rubbing sound was heard over the apex of the heart.

There was no blood in the sputum, and the patient did not appear to be much worse than when first seen, but it was decided to admit him to the hospital. Upon admission the temperature was 97° F.; respirations, 24; pulse rate, 82 and regular. The patient complained bitterly of dyspnea and orthopnea. He was obviously in respiratory distress, but he had a good color without cyanosis. The neck was normal, the upper respiratory passages were not obstructed, and the retinal vessels were normal. The lungs were resonant, with a few moist râles over both bases and without evident consolidation. The heart was normal in size, the tones were of good

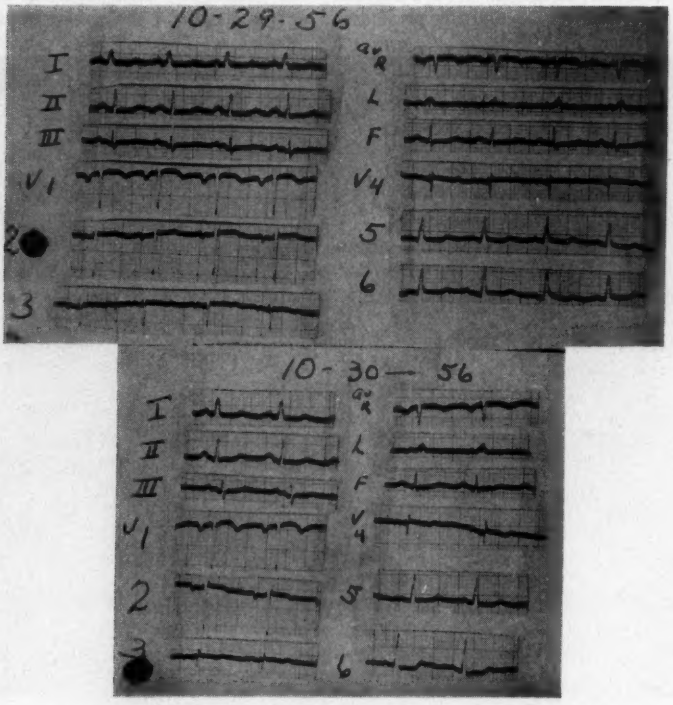

FIG. 2. Electrocardiograms, October 29 and October 30, 1956.

quality without murmurs or rub, and the pulmonic and aortic tones were normal. The blood pressure was 128/78 mm. of Hg. The liver was not enlarged, and the abdomen and extremities were normal.

Laboratory Findings: The urine was normal except for 1 plus albumin. The hemoglobin was 12.5 gm., 83%; red blood cell count, 4,300,000; white cell count, 6,000, with 64% neutrophils and 36% lymphocytes. The sedimentation rate was 16.5 mm./hr. The blood urea nitrogen measured 23 mg.%. A serologic test for syphilis (VDRL) was negative. X-ray examination of the chest revealed irregular interstitial and coalescent homogeneous densities in the perihilar region of the left lung and in both lower lung fields. The heart appeared to be normal in size and the aorta was normal (figure 1). There was no pleural effusion.

The initial electrocardiogram was abnormal, characterized by R-ST displacements and diphasic T wave changes in the precordial leads compatible with patterns observed in pericarditis with muscle injury.[3] A second electrocardiogram the following day showed the same patterns (figure 2).

Hospital Course: In view of these findings, the diagnosis was considered to be acute pericarditis probably complicating an original respiratory infection. There was no chest pain, the heart tones remained normal, no rub was heard except on one occasion, and the blood pressure stayed within normal limits. Since the patient continued to complain of severe dyspnea and orthopnea, in addition to the other measures he was treated for congestive heart failure. After 48 hours he was much better. The dyspnea had almost disappeared and the orthopnea was much better, though the patient preferred to sit upright in bed. The temperature remained normal, and there was no change in the previously recorded findings. On the morning of the third hospital day the patient felt quite well except for some dyspnea. He remained comfortable all day, ate his meals as usual and had no complaints. When he was visited by the nurse at 5:20 p.m. she noted: "The patient feels well and has no complaints." When she returned to his room 30 minutes later he was dead in bed. This was just 72 hours after admission.

Autopsy: Each pleural cavity contained a small amount of clear, straw-colored fluid. The pericardium was bluish black and was filled with clotted and fluid blood. When the blood was removed there appeared a small clot densely adherent to and protruding from the lumen of the pulmonary artery just proximal to its bifurcation. When the pulmonary artery was opened two perforations were noted which measured 0.8 cm. and 1 cm. in length, respectively. A probe introduced into these openings protruded through the artery and into the clotted area. The heart was slightly hypertrophied and weighed 550 gm. The coronary arteries were patent and the valves showed no abnormality. The left ventricle measured from 1.5 to 2 cm. in thickness, the right from 0.5 to 1 cm. in thickness. The heart valves were normal. The intima of the ascending aorta and of the arch showed numerous large, atheromatous plaques. The pulmonary artery showed a transverse linear slit at its bifurcation which completely penetrated the wall of the artery. Adjacent to the slit was a soft yellow atheromatous plaque. Sections of the pulmonary artery taken at the level of the perforation showed lipid deposition in the subintimal area. The elastic fibers in some areas were thickened and had a frayed appearance; in other areas they were completely absent. There appeared to be an increase in the glassy connective tissue present. In the adventitial zone there was recent hemorrhage, and there were small areas of hemorrhage in the wall of the pulmonary artery itself. The changes noted in the pulmonary artery at the site of the perforation were similar to those found in aortic medial necrosis.

The lungs showed no consolidation. Section of one portion of the lungs showed thickened pleura, and beneath this area the lung showed emphysema and atelectasis. The abdominal aorta was thick-walled and contained many calcified plaques. The remaining organs showed no abnormality other than some passive congestion.

Comment: * "Sections of the pulmonary artery at the level of the transverse laceration show degeneration and disruption of the elastic fibers. A van Gieson-Verhoeff stain shows degeneration, thickening, fraying and complete absence of the elastic fibers. The changes present in the pulmonary artery appear identical with those seen in aortic medial necrosis and which sometimes result in dissecting aneurysm. Several cases of rupture of the pulmonary artery have been reported usually secondary to pulmonary hypertension or severe mitral stenosis."

* Addition to the pathologic report by Dr. William A. Ehrgott, Pathology Department, Fairmont General Hospital, Fairmont, West Virginia.

Summary

1. A case is presented of spontaneous rupture of the pulmonary artery, with resultant hemopericardium and death by cardiac tamponade.

2. While no actual measurements of pulmonary pressure were made, there was no evident chronic pulmonary disease or heart disease to indicate a pre-existing pulmonary hypertension.

3. The pathologic findings suggest that the rupture was directly due to primary arteriosclerosis of the pulmonary artery.

4. The presence of the pericardial reaction was surmised, but the actual cause was not determined ante mortem.

5. Spontaneous rupture of the pulmonary artery as a result of primary atheromatous lesions will have to be considered among the many other causes of pericarditis and pericardial effusion.

6. Rupture of the pulmonary artery, with resultant cardiac tamponade, must be considered also among the causes of sudden death.

Acknowledgment

The authors express their gratitude to Dr. R. R. Rector, Surgical Department, Davis Memorial Hospital, Elkins, West Virginia, and to Dr. William A. Ehrgott, Department of Pathology, Fairmont General Hospital, Fairmont, West Virginia, for making the anatomic specimens available.

Summario in Interlingua

Le ruptura de un arteria pulmonar, sin obvie morbo pulmonar o morbo cardiac de un typo resultante in augmentos de resistentia in le circulation pulmonar, es un occurrentia plus tosto rar.

In le caso hic reportate, le patiente—un homine de affaires de racia blanc e 61 annos de etate—habeva semper gaudite de bon sanitate, excepte que ille habeva habite un minor pneumothorace spontanee in 1948. Ab isto, ille se habeva restablite completemente, e le episodio habeva habite nulle recurrentia. Le maladia que es le thema del presente reporto habeva comenciate in forma acute in octobre 1956. Illo esseva considerate, a ille tempore, como un acute infection respiratori, characterisate per un tusse sic, per malaise general, e per dyspnea. Iste symptomas se aggravava in le curso de sex dies. Al fin de iste periodo le patiente disveloppava orthopnea. Alora ille esseva hospitalisate. Al tempore de su admission al hospital, su temperatura esseva normal. Su angustia respiratori esseva obvie, sed ille manifestava nulle cyanosis. Le pulmones esseva normal, con le exception de rhonchos humide audibile supra ambe bases. Le corde esseva normal. Le tonos esseva de bon qualitate. Le pression de sanguine esseva 128/78 mm de Hg. In un examine, un sono frottante esseva audite supra le precordio. Le constatationes laboratorial esseva normal. Rontgenographia del thorace revelava densitates interstitial irregular e coalescente in le region perihilar del pulmon sinistre e in ambe campos pulmonar inferior. Le corde e le aorta esseva normal.

Le electrocardiogramma initial monstrava displaciamentos de R-ST e diphasic undas T in le derivationes precordial, de character compatibile con illo observate in pericarditis. Esseva opinate que le diagnose deberea esser pericarditis acute, probabilemente in complication de un infection respiratori original. Le tertie die de hospitalisation, i.e. le dece-prime die del maladia, le patiente—apparentemente in via de meliorar se—moriva subitemente.

Al necropsia le pericardio se monstrava replenate de sanguine coagulate e liquide, e un coagulo densemente adherente se trovava protruse ab le lumine del arteria pul-

monar, justo proximal al sito de su bifurcation. Duo perforationes esseva notate in le arteria pulmonar, de 0,8 e 1,0 cm de longor. Quando sectionate, le arteria pulmonar revelava al sito del perforationes le presentia de un deposito lipidic in le area subintimal. Fibras elastic esseva absente. Le alterationes pathologic esseva simile a illos trovate in necrosis medial aortic. Le pulmones exhibiva nulle abnormalitates significative.

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ANASARCA AND HYPOPROTEINEMIA IN RETICULUM CELL SARCOMA *

By KAYE H. KILBURN, *Denver, Colorado,* and HAROLD BROWN, *Bangkok, Thailand*

INTRODUCTION

DURING the course of treatment of a patient with reticulum cell sarcoma, a reversible syndrome consisting of anasarca and hypoproteinemia but without proteinuria was observed. Because this syndrome has not been reported previously in subjects with reticulum cell sarcoma, it is thought that the results of studies of liver and kidney function and the postmortem finding in this case merit a brief report.

CASE REPORT

A 31 year old milk route salesman entered the Salt Lake Veterans Administration Hospital on June 6, 1955, because of subcutaneous nodules of three months' duration. He had been in good health until December, 1954, when he had noted tender nodes in the left groin and left axilla. In March, 1955, he felt tiny subcutaneous nodules on his left thigh. These slowly enlarged and became erythematous and elevated. Microscopic sections of one of the nodules were interpreted as reticulum cell sarcoma. Local x-ray treatment was followed by complete regression of the lesions. In May, 1955, similar skin lesions appeared over his back, chest, abdomen and legs, and the patient developed increased fatigability. The past history and family history could not be related to this illness.

Subcutaneous nodules, ranging from 0.1 to 1.5 cm. in diameter, with erythematous surfaces, were present all over the body except the hands, feet and head. These nodules were not movable or tender, but some were ulcerated. Enlarged, firm nodes

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were palpable beneath the skin in the right epitrochlear area, the axillae and the groin. The inguinal nodes were greatly enlarged and slightly tender. The spleen was felt about 2 cm. below the left costal margin. The liver and kidneys were not palpable and no abdominal or testicular masses were present.

TABLE 1

Laboratory Examination

	6-6-55	7-20-55	8-14-55	12-26-55	1-24-56	3-4-56
Weight	164	186	147	207	160	180
Edema	0	+	0	+	0	+
Nitrogen mustard	6-16-55			1-3-56		
Blood						
VPRC	48	36	37	47, 43	39	38
WBC	6,800	2,100		8,200	2,100	3,100
Diff.	74% Poly.	95% Lym.		78% Poly.	82% Lym.	75% Lym.
Urine						
Specific gravity	1.006 1.022	1.016 1.010	1.010	1.005 1.010	1.026 1.024	1.016 1.010
Protein	0	0	0	0	0	2+
Sediment	0	0	0	0	0	10-15 WBC
Creatinine clearance		Normal				
Chemistries						
Total protein, gm./100 ml.	6.6	3.0	5.7	5.8	7.9	5.5
Albumin, gm./100 ml.	4.3	2.7	4.6	3.5	5.7	3.8
BUN, mg./100 ml.	18	19	13	16		
F. blood sugar, mg./100 ml.	77		61			
Cholesterol, mg./100 ml.	210		134, 180	146		
Sodium, mEq./L.		123, 123	137	128	139	122, 131
Potassium, mEq./L.		4.1, 3.7	4.2	4.4	4.4	
Chloride, mEq./L.		111, 105	105			116, 106
CO_2 combining power, mEq./L.		17	17, 24			9, 11
Liver Functions						
Bilirubin, d/t mg./100 ml.	0.4/1.4	0.4/0.6				
Alk. phos., units	2.1	3.2, 1.3	1.8			
Prothrombin time, sec.	14	13				
Thymol turbidity, units	3.5	4.9, 5.4				
BSP retention in 45 min.		1.0%	1.5%			
Liver biopsy		Normal				
Nitrogen balance		Normal				
Electrophoresis of serum protein		Normal				
I^{131} tagged albumin survival		Same as normal control				

The volume of packed red blood cells was 48 ml./100 ml., the red blood cell count was 5.17 million per cubic millimeter, and the hemoglobin concentration was 15.5 gm./100 ml. The white blood count was 6,800 per cubic millimeter, with 74% polymorphonuclear leukocytes, 16% lymphocytes, 7% monocytes, 2% eosinophils and 1% basophils. Other significant laboratory data are recorded in table 1. A smear of the bone marrow aspirated from the sternum showed no abnormalities. Biopsies of

the subcutaneous tissue of the abdomen and of an inguinal lymph node showed a histologic pattern characteristic of reticulum cell sarcoma.

Following the biopsies, 60 mg. (0.8 mg./Kg. body weight) of methyl-bis (beta-chlorethyl) amine hydrochloride (nitrogen mustard) were given intravenously on June 16, 1955.

On July 19, 1955, the patient had a transient episode of disorientation and incoherent speech, and was readmitted to the hospital. His weight was 186 pounds, which represented a gain of 23 pounds over his weight at the time of discharge (figure 1). His lower abdomen, thighs, legs and arms were grossly edematous. The total serum protein level was 3.0 gm. per 100 ml., of which 2.7 gm. were albumin, and the serum sodium concentration was 123 mEq./L. On subsequent days the total

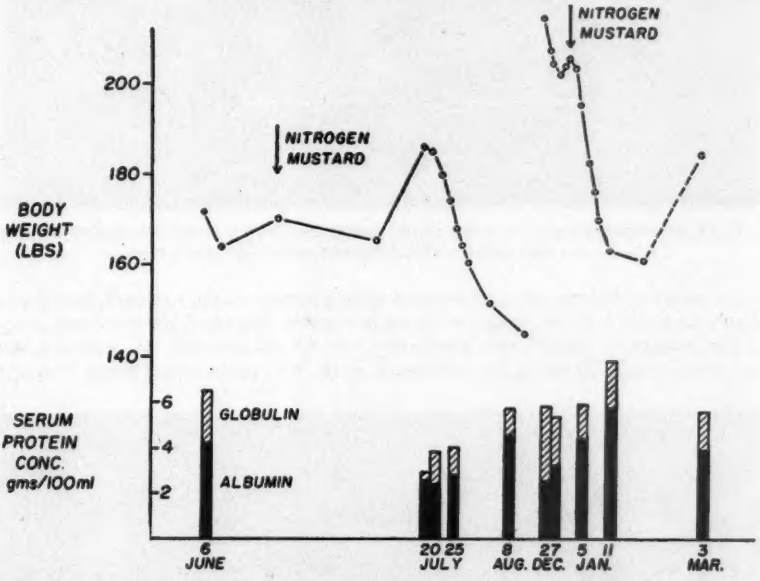

FIG. 1. The inverse relationship of the body weight and the serum concentrations of albumin and globulin is shown to be related to the administration of nitrogen mustard.

serum protein level was 3.8 gm. per 100 ml., with 2.4 gm. of albumin, and 4.1 gm. per 100 ml., with 2.3 gm. albumin, respectively (table 1). A biopsy of the liver showed normal morphology. The half-life of administered iodine^{131} labeled albumin was found to be eight days, which was the same as the half-life of this material in two normal subjects.

On August 8, 1955, after a spontaneous diuresis had reduced the patient's weight to 145 pounds, the total serum protein level had increased to 5.7 gm. per 100 ml., of which 4.6 gm. were albumin, and the serum sodium concentration was 137 mEq./L. (figure 1). At this time a 10-day balance study showed that there was a negative nitrogen balance of less than 1 gm. per day. No proteinuria was noted during this period.

The patient returned to work until December 16, 1955, when he again developed progressive edema and enlarging skin nodules. On admission to the hospital 10 days

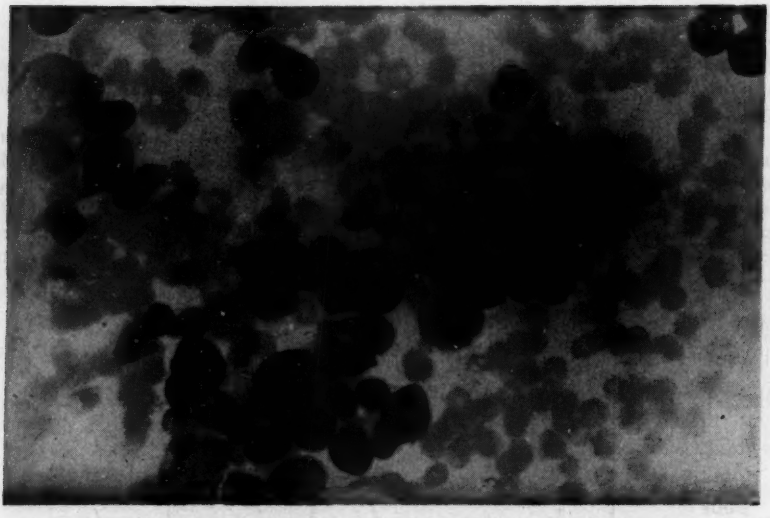

FIG. 2. A photomicrograph of a smear of the peripheral blood one day before death, showing clumps of large, pleomorphic reticulum cells (Wright's stain).

later he weighed 214 pounds, and marked pitting edema of the extremities and trunk and subcutaneous nodules similar to those previously described were present.

The volume of packed red blood cells was 47 ml. per 100 ml., and the white blood count was 8,200 per cubic millimeter, with 78% polymorphonuclear leukocytes

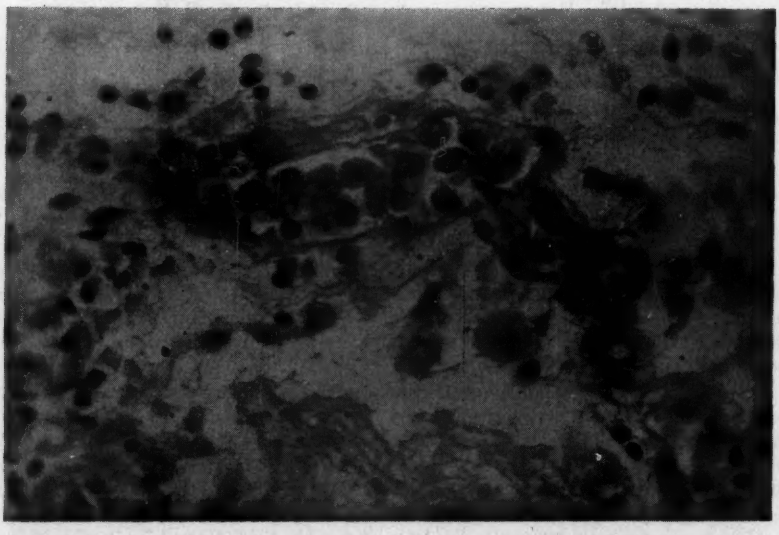

FIG. 3. A high power view of a pulmonary alveolar capillary in longitudinal section filled with large mononuclear tumor cells (hematoxylin and eosin 440 ×).

FIG. 4. Photograph of a kidney showing the pale thickened cortex, bulging capsule and increased size which resulted from diffuse infiltration by tumor.

and 18% lymphocytes. The urine specific gravity was 1.026 and 1.024. There was no albuminuria. The total serum protein level was 5.8 and 5.5 gm. per 100 ml., with the albumin 3.5 and 3.2 gm. per 100 ml., respectively. The serum sodium concentration was 128 mEq./L. (table 1). An intravenous pyelogram showed poor concen-

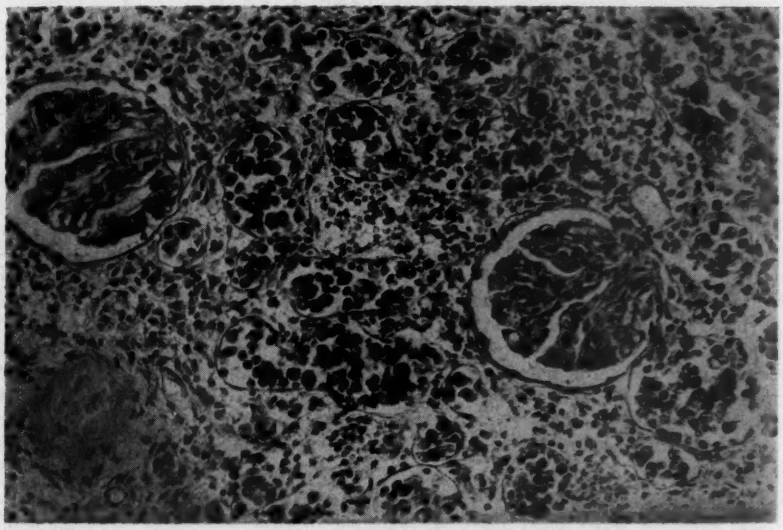

FIG. 5. A photomicrograph of a section of the renal cortex showing tumor cells in glomeruli, tubules and blood vessels (hematoxylin and eosin 200×).

tration of the dye, with adequate visualization of only the superior calyces bilaterally, but no other abnormalities.

Salt restriction, ammonium chloride and mercurial diuretics failed to produce a diuresis and, on January 3, 1956, 45 mg. of nitrogen mustard, 0.6 mg./Kg. of body weight, were given. A diuresis began promptly and the patient's weight dropped from 205 to 163 pounds during the following week.

The patient was admitted for the last time in late February, 1956, because of the appearance of enlarging nodules on his neck and back. Subsequently, he complained of progressive fatigue, anorexia, nausea, vomiting of food, watery diarrhea, shortness of breath, dizziness and joint stiffness.

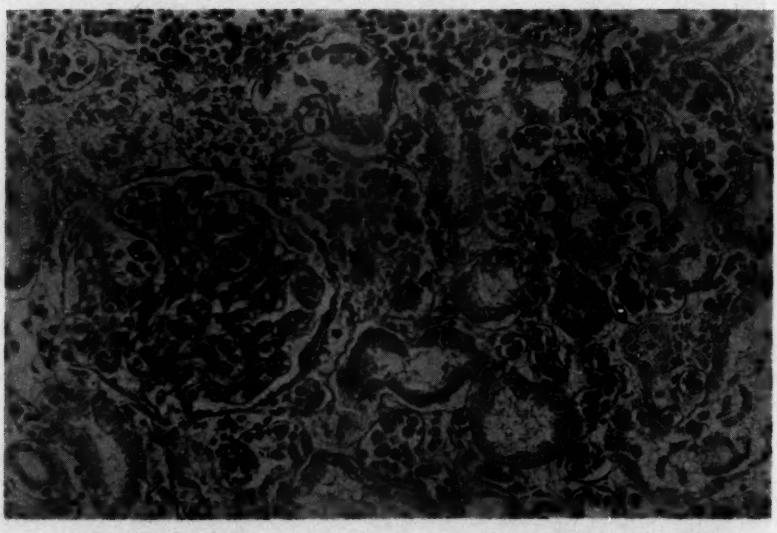

FIG. 6. A higher power view of the renal cortex showing interstitial and intracapillary tumor cells compressing tubules, vessels and a glomerulus (hematoxylin and eosin 440 ×).

Although he weighed 180 pounds, he appeared dehydrated. Generalized small subcutaneous nodules were present. His respirations were 24 per minute and were shallow and labored. The heart rate was 112 per minute, and the blood pressure 95/50 mm. of Hg. The lungs were clear to percussion and auscultation. No cardiac murmurs were heard. The liver was palpable 6 cm. below the right costal margin. At this time the total serum protein level was 5.5 gm. per 100 ml., with 3.8 gm. per 100 ml. albumin (table 1), and the serum sodium concentration was 122 mEq./L. Clumps of large undifferentiated cells, which stained a deep blue and had prominent nucleoli, were present in smears of the blood (figure 2). An electrocardiogram showed low amplitude of the QRS complexes and sinus tachycardia. The patient was cyanotic and appeared acutely ill.

He was treated with oxygen, digitalis, intravenous fluids, whole blood, arterenol and prednisone, but there was no improvement. He died the day following admission after developing oliguria, extreme dyspnea and a fever of 102° F.

Postmortem Findings: The body was markedly edematous and had numerous subcutaneous nodules. Slight accumulations of fluid were present in all the serous cavities. The heart was soft and dilated. The cut surface of the myocardium

showed yellowish patches of tumor, and the microscopic examination revealed marked myocardial replacement by reticulum cell sarcoma. The right lung weighed 1,280 gm., the left 1,100 gm. The lungs were of a firm consistency, and the cut surfaces were hemorrhagic and edematous. Microscopic examination showed many alveolar capillaries filled with tumor cells (figure 3). The liver weighed 2,480 gm. and was completely uninvolved by tumor infiltrates, although a few blood vessels contained anaplastic reticulum cells. Retroperitoneal tumor was not present.

The kidneys were of normal contour and weighed 330 gm. each (figure 4). There was no ureteral obstruction or dilation of the collecting systems. Vasa recta, proximal and distal tubules and many glomeruli were surrounded, invaded or in small areas completely replaced by pleomorphic reticulum cells containing many mitoses (figures 5 and 6). A few small subcapsular scars were present.

Sections of the pituitary, thyroid and adrenals showed infiltration by tumor, and the parenchyma of the spleen, lymph nodes and bone marrow was partially replaced by tumor cells.

Discussion

It is recognized that anasarca and hypoproteinemia may be associated with congestive heart failure, glomerulonephritis and advanced hepatic cirrhosis.[1] In addition, there remains a diverse collection of cases which are grouped together as idiopathic hypoproteinemia and edema. Recently, newer investigative technics have demonstrated evidence suggesting decreased protein synthesis in some of these cases,[2, 3] while others show an accelerated rate of protein breakdown.[3-6] Other cases are attributed to hepatic atrophy or fatty change,[3] copper deficiency,[7] pancreatic insufficiency [8] or primary aldosteronism.[9] Inflammatory or neoplastic infiltrates in the kidney, in addition to the well characterized nephrotic syndromes associated with amyloidosis or renal venous occlusion, have also been associated with hypoproteinemia and edema.

Illingworth and Finch in a recent review [3] described a series of children with hypoproteinemia and edema who were, however, in positive nitrogen balance. They had been presumed to have a defect in protein synthesis. Postmortem sections from the livers of these patients showed cellular atrophy or diffuse fatty change.

Hypocupremia, iron deficiency anemia, hypoproteinemia and edema characterized five infants studied by Sturgeon and Brubaker.[7] These infants had been sustained on a diet of milk which was free of copper. These abnormalities reverted to normal on a regular diet which contained an adequate quantity of copper and iron. Ulstrom, Smith and Heimlich [5] also noted hypocupremia in three of four infants who had been eating allegedly adequate diets. These children manifested edema, pallor and irritability, and were found to have anemia and hypoproteinemia. The concentrations in the serum of albumin, alpha 1, alpha 2 and gamma globulin were decreased. The turnover of phenylalanine-3-C^{14} in the plasma was increased, however, as indicated by an accelerated disappearance rate of this material in the three infants studied when they were compared to two normals. Oral iron and nitrogen balances were both positive. These authors attributed the hypocupremia to a decrease in the copper-binding alpha-2-globulin fraction of the serum protein. This syndrome disappeared after varying periods on routine hospital diets. These authors concluded that a "cellular level defect in protein metabolism" was responsible for the rapid degradation of proteins suggested by their studies.

Albright [4] reported a 19 year old boy who had a two-year history of edema and hypoproteinemia without proteinuria. Results of hepatic and renal function studies were normal, as was the histology of the liver. An intravenous albumin balance study showed an increased rate of destruction of injected human albumin, as manifested by increased nitrogen and phosphorus excretion.

Steatorrhea was demonstrated by fat balance tests in two children with hypoproteinemia and edema studied by Illingworth and Finch.[8] One child who died showed fatty change in the liver and extensive fatty infiltration and atrophy of the pancreatic acini. Two other children with transient edema and hypoproteinemia failed to show abnormalities of pancreatic function. Recovery appeared to be spontaneous, and the syndrome was attributed to a temporary disturbance of protein metabolism of unknown cause.

Primary aldosteronism has been associated in several cases [9] with anasarca and a relative hypoproteinemia due to extracellular dilution. Removal of adrenal cortical tumors has been corrective of both the edema and the hypoproteinemia.

Many reports [10, 11, 12, 13] have dealt with neoplastic renal infiltration in patients with leukemia or lymphoma. Various clinical findings have been described associated with diffuse bilateral involvement. A few reports [11, 14, 15] have mentioned edema, particularly during the terminal phase of the illness. Odell and Popp [16] described three patients with lymphosarcoma who had edema and albuminuria. The presence of large renal shadows and poor excretion of contrast media suggested a diagnosis of renal lymphomatosis. One patient had hypoproteinemia. Temporary remissions of the edema and albuminuria followed irradiation to the kidneys. Unfortunately, autopsy studies were not reported.

The patient herein reported gave no history suggestive of inadequate intake of protein or copper, and no clinical evidence of malnutrition was present. Thus it would be difficult to explain his hypoproteinemia on a nutritional basis. Although the concentration of the serum proteins was decreased, electrophoresis revealed a normal distribution of the fractions, which would be hard to reconcile with a defect in protein synthesis. Increased catabolism of protein appears unlikely because the decay curve of the radioactive iodine-tagged albumin administered to this patient was similar to the decay curve in two normal subjects. The investigations of hepatic function detailed previously (table 1), the normal histologic appearance of a liver biopsy eight months before death and the normal liver at autopsy suggest that the hypoproteinemia could not be attributed to liver disease. The lack of cystic fibrosis or atrophy of acini makes significant pancreatic insufficiency improbable. The normal serum potassium concentration despite marked fluctuations in the serum sodium and chloride levels and the absence of an adrenal tumor make primary aldosteronism unlikely.

Although this patient failed to fit into any well characterized nephrotic syndrome, the diffuse bilateral renal infiltration by tumor would suggest that a renal mechanism had produced the remitting anasarca and hypoproteinemia. These infiltrates could have raised the renal tissue pressure and obstructed the circulation. This resulted in a re-absorption of sodium, chloride and water by the renal tubules, and consequent dilution of the body fluid compartments. The spontaneous diuresis which ended the first period of anasarca may have represented an adjustment to this alteration in circulatory dynamics produced by the tumor.

The second diuresis, which occurred immediately following therapy, may have been due to destruction by nitrogen mustard of the tumor cells. It is postulated that this treatment relieved the mechanical interference to the renal circulation and produced the prompt diuresis and rapid restitution of serum protein, sodium and chloride concentrations.

In the absence of tachycardia, cardiac dilatation, a palpable liver and pulmonary edema during two episodes of remitting anasarca, primary myocardial failure was considered unlikely. However, the marked myocardial replacement by tumor and the tumor infiltration (figure 3), congestion and edema of the lungs at the time of death strongly suggest that myocardial failure played a major role in the third (terminal) episode.

In conclusion, the results of these studies suggest that a primary renal tubular abnormality was produced by the reticulum cell sarcoma infiltrate which resulted in fluid and electrolyte retention, evidenced by anasarca and hypoproteinemia.

Summary

Remitting anasarca and hypoproteinemia without proteinuria developed on two occasions in a patient with reticulum cell sarcoma. One remission was apparently spontaneous. The second followed therapy with nitrogen mustard. Hepatic and renal function tests, a nitrogen balance study, electrophoresis of serum proteins and I^{131} albumin turnover rate were all normal. At autopsy, marked renal infiltration by reticulum cells was found. It is postulated that increased renal tissue pressure and reduced renal blood flow resulted from neoplastic infiltration. This, it is suggested, produced retention of water and electrolytes and eventuated in hemodilution and edema.

Acknowledgment

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Summario in Interlingua

Un syndrome de character reversibile, consistente de anasarca e hypoproteinemia sin proteinuria, esseva observate in un juvene masculo con sarcoma a cellulas reticular. Le prime periodo de anasarca se terminava in diurese spontanee. Un secunde e simile periodo se terminava in un diurese que sequeva promptemente le administration parenteral de mustarda de nitrogeno. Le patiente moriva durante un tertie episodio de anasarca associate con cyanose e congestive insufficientia cardiac. Le examine microscopic revelava cellulas tumoric reimplaciante extensemente le myocardio e le renes e obstruente multe capillares pulmonar e systemic.

Le causa del anasarca e hypoproteinemia non esseva identificate in le curso del examines routinari laboratorial e roentgenologic e de studios special que includeva biopsia hepatic, electrophorese de proteinas seral, determination del periodo de medie valor de albumina human marcate con I^{131}, e un studio de balancia de nitrogeno.

Viste que iste patiente non exhibiva indicios de defectos que es cognoscitemente capace a reducer le synthese o a augmentar le destruction de proteina ben que rapide alterationes esseva evidente in le concentrationes de proteina e del electrolytos—alterationes coincidente con alterationes de peso—il esseva postulate que le anasarca

e le hypoproteinemia esseva effectuate per un mechanismo renal. Iste hypothese trovava supporto in le constatation de massive infiltrationes de cellulas tumoric in ambe renes. Le prime diurese esseva possibilemente le resultato de un adjustation spontanee al alteration producite in le circulation renal per un infiltration neoplastic, durante que le secunde diurese resultava possibilemente ab le destruction de cellulas tumoric que habeva augmentate le pression del histos renal, obstruente assi le circulation renal. Es suggerite que le elimination de iste obstruction mechanic permitteva le occurrentia de diurese, le qual produceva un prompte restitution del concentrationes seral de proteina, natrium, e chloruro.

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EDITORIAL

CARDIAC DISTURBANCES DURING THE PANDEMIC OF INFLUENZA OF 1918 to 1920

ALTHOUGH the recent pandemic of influenza has proved mild and has shown thus far a much lower mortality than that of 1918 to 1920, there has been a substantial increase in general mortality rate at the peaks of the epidemic, and it is by no means a negligible disease. Furthermore the tendency of previous pandemics to recur in waves one, two, and even three years after the initial onslaught and the frequent observation of greater severity during the recurrences [1] should warn against too great complacency as yet regarding the current epidemic. Observations made during previous pandemics with some limitations are still worthy of consideration.

The clinical illness suffered by a patient with influenza depends not merely upon the virulence of the strain of virus concerned and upon its direct ravages but even more upon the secondary bacterial infections to which the subject has been made hypersusceptible. These invaders vary from time to time and place to place, accounting for many of the differences in the clinical picture which have been described. In general during the pandemic of forty years ago the respiratory system bore the brunt of these attacks, and the secondary pneumonias were responsible for the high mortality. In most subjects this quite overshadowed the injury suffered by other organs and systems, although these did not escape entirely unscathed.

In an acute infection with a high mortality, the question of the immediate outcome often centers on the condition of the circulatory system. Central or even more often peripheral circulatory failure is commonly the immediate cause of death. In the former pandemic this was not conspicuously the case until the very terminal stage of the illness. Circulatory and particularly cardiac disturbances commonly attracted scant notice.

The most frequently observed circulatory disturbance was a bradycardia quite similar to that observed in typhoid fever. During the febrile stage as a rule the pulse rate was relatively much less increased than the respiratory rate or the temperature, and during convalescence bradycardia often became marked. In the fulminant cases and those running an unfavorable course, tachycardia developed as a late or subterminal feature. Many regarded a rate of 120 or more as a grave omen if maintained for any notable period.[2, 3]

The blood pressure was ordinarily low. In severe cases there was

[1] Greenwood, M.: The epidemiology of influenza, Brit. M. J.: 1: 563–566, 1918.
[2] Cole, C. E. C.: Influenza epidemic at Bramshott in September-October, 1918, Brit. M. J. 2: 566–568, 1918.
[3] Hart, T. S.: The heart in bronchopneumonia, Am. J. M. Sc. 158: 649–658, 1919.

marked congestion of the tissues generally, a deep cyanosis, a "blue pneumonia," doubtless aggravated by pulmonary edema and profuse bronchial secretion, but attributed by some to a severe "toxemia" rather than to asphyxia.[4]

As to the heart itself, any primary gross injury seems to have been exceptional. At autopsy, some dilatation, especially of the right side, was commonly observed, with diffuse changes such as "cloudy swelling," evidence of "parenchymatous degeneration," loss of striation, but usually no clearcut inflammatory changes.[5, 6]

Most clinical descriptions are in harmony with these observations. Mackenzie [7] regarded the changes seen in most cases as identical with those commonly met with in other febrile infections, subsiding promptly with recovery. In severe cases he recognized more serious damage to the myocardium by fever and "toxins," with hypotension, cyanosis, increasing tachycardia, a small "thready" pulse, muffled heart sounds, systolic murmurs. Death, however, he attributed to intoxication of the tissues generally and not to primary cardiac injury. He stated that he had never seen a case of influenza in which damage was limited to the heart alone, in which influenza had initiated a progressive myocarditis, or in which it had adversely affected a patient with preëxisting chronic heart disease. Reports from many American Army Camps were in general in accord with this.[8]

Mackenzie did not attribute to cardiac injury the protracted convalescence with asthenia, palpitation, precordial pain, dyspnea and tachycardia on slight exertion. This was rather attributed to vasomotor disturbances secondary presumably to injury to the nervous system, and as an indication for "judicious exercise" rather than for rest and digitalis. He did mention one case showing during convalescence a partial (2 to 1) heart block with delirium or syncope during the periods of bradycardia, but with subsequent complete recovery.

Some other observers, however, found more definite evidence of cardiac injury. Thomas Lewis [9] regarded influenza as a menace to the heart, particularly in patients with chronic cardiac disease. When the infection spread to a ward reserved for such cases, two deaths attributable to influenza soon followed and several others were seriously jeopardized.

The most convincing evidence of cardiac injury was found in limited groups of patients who showed certain arrhythmias and disturbances of

[4] Synnott, M. J., and Clark, E.: The influenza epidemic at Camp Dix, N. J., J. A. M. A. 71: 1816–1821, 1918.

[5] Lucke, B., Wight, T., and Kime, E.: Pathologic anatomy and bacteriology of influenza (1918), Arch. Int. Med. 24: 154–237, 1919.

[6] The Influenza Committee of the Advisory Board to the D. G. M. S., France: The influenza epidemic in the British Armies in France, Brit. M. J. 2: 505–509, 1918.

[7] Mackenzie, J.: The cardiac complications of influenza, Practitioner 102: 19–25, 1919.

[8] Friedlander, A., McCord, C. P., Sladen, F. J., and Wheeler, G. W.: The epidemic of influenza at Camp Sherman, Ohio, J. A. M. A. 71: 1652–1656, 1918.

[9] Lewis, T., quoted by Hamburger.[15]

conduction, particularly those reported by Cockayne.[10] He found bradycardia "extremely common" in "hundreds of cases" admitted to the Royal Naval Hospital at Haslar, with a rate under 60 in a majority after the temperature fell to normal. He had notes on 132 cases with pulse rates under 50, in some as low as 36. In one man of 18 he observed a normal temperature, a pulse rate of 44 and a respiratory rate likewise of 44. Of 55 of these from whom he obtained polygrams, there was a partial block in 19. Some showed a prolonged a–c interval, some a "sinus block," with dropped beats. Nine cases showed a 2 to 1 block, and six a 3 to 1 block. These abnormalities cleared up after an average duration of 14 days, often with marked irregularity of the pulse during this period. He noted one case with a 2 to 1 block alternating with auricular extrasystoles, with corresponding pulse rates of 36 and 78. One older man with fibrillation (untreated) had a pulse rate of 44. He was unable to differentiate a simple bradycardia which might be as slow as 36 from block except by a tracing. The rate was but little affected by large doses of atropin, which was also the experience of many other observers. He attributed both the bradycardia and the block to the action of the same "toxin" on the myocardium and not to increased vagal tone. A striking feature was the complete and usually prompt recovery from these abnormalities in most cases.

This, however, was not invariable. Flöystrup,[11] who remarked on the rarity (in Scandinavia) of reports of actual heart disease, described one case in a man of 26, who showed subjective and clinical evidence of cardiac weakness with abnormalities in the electrocardiogram which cleared up only after 16 weeks. There was no bradycardia or block in this case.

Hart [3] in a series of cases of bronchopneumonia, largely post-influenzal, found the heart relatively spared in most. In cases progressing unfavorably there were cyanosis, subterminal acceleration and arrhythmia attributed to a "general toxemia." As many others have reported, such patients gave no response to digitalis. Those who came to necropsy showed only "moderate" myocardial degenerative changes.

Sabshin [12] was more impressed by evidence of myocardial injury in the severely ill patients he observed. The bradycardia was "remarkable," in one subject with a temperature of 40° C., the pulse rate was 90. With this he described a low blood pressure, arrhythmias, feeble altered heart sounds, murmurs, a diffuse apex beat, precordial pain, cyanosis, and late acceleration. He noted a marked lability of the pulse rate, which in convalescence might rise from 50 to 100 on walking across the room. The bradycardia was not affected by atropin.

[10] Cockayne, E. A.: Heart-block and bradycardia following influenza, Quart. J. Med. 12: 409, 1918–19.

[11] Flöystrup, G.: Ectopic auricular systoles in a case of influenza-myocarditis, Acta med. Scandinav. 53: 866–871, 1920.

[12] Sabshin, Z. I.: Circulatory complications in influenza, New York M. J. 109: 635, 1919.

Curtis [13] made similar observations, noting well marked bradycardia in 20 per cent of his cases, with a rate as low as 30 during convalescence, not influenced by atropin. In severe cases he observed dilatation, especially of the right auricle, at autopsy, which he attributed to a "toxic" action on the myocardium and to the effects of pulmonary congestion and edema, copious bronchial secretion and exhausting cough.

Cumston [14] described similar alterations in patients observed during the pandemic in Geneva, Switzerland. Bradycardia, averaging 40 to 50, was observed at all stages of the disease. One pulse rate was recorded as 15 (not further characterized). In the severe cases a "myocarditic syndrome" developed (without necessarily showing visible changes in the muscle at necropsy), the pulse rate became unstable, with extrasystolic arrhythmia, hypotension, feeble beats, and he observed with unusual frequency severe acute precordial or retrosternal pain with a sense of pressure or torsion and many anginoid features.

Hamburger [15, 16] reported observations with a late followup of eight illustrative cases showing disturbances of cardiac function which persisted long into convalescence. In addition to subjective complaints, in general they showed a labile or rapid pulse rate, a poor response to exercise, electrocardiographic changes, arrhythmias with either auricular or ventricular premature beats or "ectopic auricular extrasystoles," and disturbances of conduction—partial block or bundle-branch block. In the later followup, only one of the six found still showed abnormalities, tachycardia and auricular extrasystoles. He concluded that the effects on the heart are transitory.

Hyman [17, 18, 19] also reported cardiac disturbances, chiefly bradycardia of 60 or less and heart block, during or following influenza. He stated that this had been brought to his attention by Rehfish in Berlin. Although his observations seem to have been made after the height of the pandemic had passed, it seems likely that most of his cases had real influenza. He found instrumental means necessary to differentiate these conditions in many cases. Simple bradycardia showed a regular rate and a normal electrocardiogram. There were varying degrees of reduction of conductivity, some showing merely a prolonged P-R interval. With a rate of 40 to 50 there was usually some irregularity with "escaped sinus-nodal beats." With a rate below 40 these escaped beats became more numerous, and in some of the most marked cases complete block occurred with a ventricular rate of about 44. Occa-

[13] Curtis, G. P.: Cardiac sequelae of influenza, J. M. Soc. New Jersey **17**: 45–48, 1920.
[14] Cumston, C. A.: Cardiac manifestations in influenza, New York M. J. **112**: 857, 1920.
[15] Hamburger, W. W.: Involvement of the auricle and conduction pathways of the heart following influenza, Am. J. M. Sc. **160**: 479–491, 1920.
[16] Hamburger, W. W., and Priest, W. S.: Structural and functional involvement of the heart following respiratory and other infections, Am. J. M. Sc. **166**: 629, 1923.
[17] Hyman, A. S.: Postinfluenzal heart block, M. J. and Rec. **124**: 698–703, 1924.
[18] Hyman, A. S.: Postinfluenzal disturbances of the heart, New York State J. Med. **26**: 1022–1024, 1926.
[19] Hyman, A. S.: Postinfluenzal bradycardia, Arch. Int. Med. **40**: 120–127, 1927.

sionally flutter or auricular fibrillation was observed. The outlook for eventual recovery was good except in cases with complete block or gross disturbances of rhythm. There was not necessarily a good correlation between degree of the cardiac disturbance and the apparent severity of the infection.

He found the frequency of "cardiovascular disturbances" to be 12 per cent of 231 cases seen at Long Island (Boston) Hospital earlier in the epidemic, but only 4 per cent in 1925 to 1926 among a younger group with less severe infections. He stated that Rehfish estimated that the frequency was 7 per cent in Berlin, and that Parson-Smith found 5 per cent in London. Such figures mean little without precise criteria for the selection of the cases.

Several other single case reports of patients showing similar disturbances of conduction were found.[20]

Lukdes and Waltner [21] (Germany) and Lebedev [22] (Moscow) reported evidence of temporary cardiac injury in children with influenza, based upon clinical symptoms and evidence of some cardiac dilatation, confirmed by x-ray. It seems questionable whether this is much more than the protracted convalescence often seen in adults. No report of electrocardiographic studies in these cases was found.

A critical appraisal of these reports indicates that they are open to criticism in several respects. Instrumental, especially electrocardiographic examinations are often lacking or inadequate, although in many the observations regarding arrhythmias and the presence of block seem dependable. The diagnosis of influenza, based entirely on clinical grounds as it still largely is, may have been inaccurate in some. It is quite impossible clinically to dissociate the injury due to the virus from that caused by the bacterial secondary invaders. Indeed in the severe cases the latter usually dominate the picture and the details might well differ from one another in the case of pneumococcal, hemolytic streptococcal or hemophilus infections. The latter two limitations would apply with almost equal force to similar studies at the present time.

With these limitations in mind some tentative conclusions may still be reached. In the great majority of cases of influenza as it was recognized clinically the heart did not suffer any significant primary injury unless the simple bradycardia (with normal electrocardiogram) which does not respond to atropin is regarded as a sign of such injury. Death was attributable to the effects of the infection on the organism generally, with involvement of the cardiovascular system in the terminal stages, manifesting peripheral collapse and a state of shock rather than direct myocardial injury. In a minority of cases the myocardium seemed adversely affected. In some cases

[20] Taub, S. J.: Heart block following grippe infection, Illinois M. J. 49: 487–498, 1926.
[21] Lukdes, J., and Waltner, K.: Postgrippale Herzdilatation im Kindesalter, Monatschr. f. Kinderh. 31: 72–73, 1926.
[22] Lebedev, D.: Postgrippale Herzdilatation im Kindesalter, Monatschr. f. Kinderh. 32: 237–238, 1926.

the development of "irritable foci" resulted in extrasystolic arrhythmia, either auricular or ventricular. More characteristic was impaired conductivity, which might cause merely a prolonged P-R interval or with notable bradycardia result in some "escaped" beats. Partial block (1 to 2, 1 to 3, 1 to 4) was not uncommon. Complete block occurred but it was exceptional and was regarded as ominous, as was flutter or fibrillation. Milder degrees of block, however, usually subsided fairly promptly if the patient survived the infection. Rarely signs of injury might last for many months or even two or three years, but the ultimate outlook was usually good. The respiratory infections determined the outcome in most cases, and this still seems to be true today.

PAUL W. CLOUGH

REVIEWS

Biochemical Disorders in Human Disease. Edited by R. H. S. THOMPSON, M.A., D.M., Professor of Chemical Pathology, University of London (Guy's Hospital Medical School), and E. J. KING, Ph.D., F.Sc., F.R.I.C., Professor of Chemical Pathology, University of London (Postgraduate Medical School). 843 pages; 25 × 16 cm. Academic Press, Inc., New York. 1957. Price, $12.60.

Over thirty contributors, well known in their respective fields, have gathered the widely scattered literature concerned with various biochemical abnormalities associated with human disease to present a summary in a practical and clinically oriented fashion. The material is arranged on the basis of 'organ systems' rather than on the more usual basis of disorders in carbohydrate, fat and protein metabolism. The following groups of diseases are discussed: gastrointestinal, renal and genitourinary, hypertensive, hematologic, neurologic, nutritional and endocrine. Six additional chapters are devoted to miscellaneous metabolic disorders: abnormalities of amino-acid and hemoglobin metabolism, connective tissue disorders, porphyrias, hemochromatosis, glycogen storage diseases, lipidoses and disorders of the reproductive system.

This should be a useful reference for the medical student, the scientifically minded clinician, and the investigator.

M. A.

Pediatric Cardiology. By ALEXANDER S. NADAS, M.D., F.A.A.P., Assistant Clinical Professor of Pediatrics, Harvard Medical School; Cardiologist, The Children's Hospital, etc. 587 pages; 24.5 × 16 cm. W. B. Saunders Company, Philadelphia, Pennsylvania. 1957. Price, $12.00.

Pediatric cardiology is a relatively new field, and there has been a paucity of good texts to cover the developments in this rapidly expanding branch of medicine. This text considers diagnostic methods, and describes the various types of acquired and congenital heart disease. It is, as the author states, a personalized text with primary emphasis on the principles and procedures in the clinical recognition and management of heart disease in children, and is intended for the pediatrician, the general practitioner and the medical student. Such a personalized text has limitations as well as advantages. While there are statements with regard to diagnosis and treatment with which the clinical reviewer may disagree, the author's attitude is candid; where his experience is limited, he so states and he points out where his opinion "is based more on faith and impression than on factual data." The diagrams are good, but one regrets in a text of this size the absence of any illustrations on the embryology of congenital heart diseases. This volume fulfills the author's purposes admirably and is well organized and carefully written.

SIDNEY SCHERLIS, M.D.

Tuberculosis in White and Negro Children. In 2 volumes. By JANET B. HARDY, M.D.C.M., and MIRIAM E. BRAILEY, M.D., Dr.P.H. 122 pages (Volume I), 103 pages (Volume II); 29 × 22 cm. Published for the Commonwealth Fund by the Harvard University Press, Cambridge, Massachusetts. 1958. Price, $7.50 (Vol. I), $4.50 (Vol. II).

As the famous paper of Roper and Waring is to the significance of "idiopathic" pleural effusion, so is this work to the significance of untreated tuberculosis of childhood.

This monumental study is based on data derived from the records of 1,329 children treated in the Tuberculosis Clinic of the Harriet Lane Home of the Johns Hopkins Hospital. Cases were admitted to the study from 1928 to 1944, and follow-up was continued until completion of compilation of records in 1950.

The first volume, by Dr. Hardy, "The Roentgenologic Aspects of the Harriet Lane Study," presents a large collection, admirably reproduced, of x-rays demonstrating the various manifestations of childhood tuberculosis and its course towards healing or progression. Differential features of similar diseases are also shown. A second section of this volume deals with the procedures of bronchoscopy and bronchography in children with a detailed treatment of indications and technics.

The second volume, by Dr. Brailey, "The Epidemiologic Aspects of the Harriet Lane Study," considers in detail the significance of the various presenting manifestations of childhood tuberculosis not subsequently influenced by present-day chemotherapy.

The younger the child the more frequent and more serious were the chest lesions demonstrated at initial examination, the greater were the extra pulmonary complications and mortality. In almost all respects the situation was considerably more grave for Negro children than for the white.

The likelihood of development of reinfection type phthisis was much greater in Negro children, with a high mortality from progression of the pulmonary process. In this respect the outlook was much more serious for girls, and the significance of age was reversed, the development of phthisis being roughly twice as frequent if the child were found to be infected between the ages of three and fifteen as it was for a child whose primary infection was discovered before the third birthday. Evidence is presented that exogenous reinfection does play a role in the development of reinfection type pulmonary tuberculosis.

These volumes will be of great interest to all concerned with tuberculosis.

PATRICK B. STOREY, M.D.

Diagnostic Medical Parasitology. By EDWARD K. MARKELL, Ph.D., M.D., and MARIETTA VOGE, M.A., Ph.D. 276 pages; 24 × 16 cm. W. B. Saunders Company, Philadelphia. 1958. Price, $7.00.

As outlined in the foreword, the purpose of this book is to present to the medical student or clinical laboratory technician the essential facts and most reliable methods needed for the laboratory diagnosis of parasites of medical importance. Not only does this text accomplish its aim as a laboratory manual, but it presents, in an excellent, concise manner, the life histories of the organisms and also the pathogenesis, clinical picture and epidemiology of the various disease states. Thus the book will well serve as an excellent adjunct to lecture material.

The authors feel that medical parasitology should not be presented in a phylogenetic fashion; rather, they discuss the various parasites in relation to the organ systems affected. Following an introductory section on host-parasite relationships are chapters devoted to intestinal protozoa and helminths, blood parasites, parasites of the genito-urinary tract, tissue parasites and medically important arthropods. In addition to a chapter on special diagnostic methods (animal inoculation and serological tests) and a chapter on fixatives and stains, there are excellent discussions of the procedures of examination of stool and blood which precede the chapters on intestinal and blood parasites. A chapter entitled "Pseudoparasites and Pitfalls" should be rewarding to the student, although it would have been of greater advantage following, or included in, the chapter on stool examination.

In addition to being a very readable text, it is amply illustrated by simple well described drawings, charts, photographs and color plates. Summary characteristics

of suggestive and diagnostic importance are presented for the intestinal protozoa as simplified keys to the helminths and microfilarias. The only failing one can find is the paucity of information on immunity to parasitic infections, which is touched upon lightly in the chapters on parasitism and special diagnostic methods. The authors also felt that the therapy of the various diseases is best presented to the student in courses of medicine and therapeutics, and therefore is not covered in the text. For what has been designed as a text and laboratory manual for medical students and technicians, this book will be difficult to surpass.

B. H. S.

Polymyositis. By JOHN N. WALTON, M.D., M.R.C.P., and RAYMOND D. ADAMS, M.D. 270 pages; 22.5 × 14.5 cm. The Williams and Wilkins Company, Baltimore. 1958. Price, $7.00.

Disorders of muscle have received much attention in the medical literature in recent years. The profusion of clinical, descriptive terms defining muscle syndromes has done little to assist in codifying muscle diseases or in clarifying their relationships to one another. The present book analyzes one class of muscle disease, "idiopathic" polymyositis, and represents an attempt to establish this as a separate entity on rational, scientific bases.

The authors have designated as polymyositis several types of muscle disorders because of similarities in histological appearances and electrical behavior. Subdivisions of the class have been based on clinical pictures in the main. The case for including polymyositis in the collagen group of diseases is strongly presented, and indeed some of the collagen diseases which involve muscle to a greater or lesser degree are considered variants of polymyositis. Forty patients with polymyositis, seen by the authors, form the basis for this monograph. Each case is summarized in an appendix. Muscle biopsy material from these patients is extensively reviewed, and many photomicrographs are reproduced to embellish the arguments and discussions in the text. The literature is critically reviewed and case material from other authors has been used to amplify or support the positions taken. Some of the premises are admittedly tentative, and further study is necessary to verify or refute the validity of the classification and of the conclusions.

Drs. Walton and Adams have produced a stimulating and informative monograph. Though at first glance the subject seems limited, this is not a book aimed at the specialist in neuromuscular diseases. It is lucid, persuasive, and broad in scope, suitable for the internist, pathologist, and other interested physicians. A successful attempt has been made to clarify some muscle disorders.

JEROME E. COHN, M.D.

Fundamentals of Neurology. 3d Ed. By ERNEST GARDNER, M.D., Professor of Anatomy, Wayne State University College of Medicine, Detroit. 388 pages; 22.5 × 14.5 cm. W. B. Saunders Co., Philadelphia. 1958. Price, $5.75.

This is the third edition of this text which is primarily a neuroanatomy text with a clinical orientation. This orientation has led the author to stress those structures which are of current clinical interest. The author has also discussed physiologic aspects where this appears necessary to relate neuroanatomy to clinical problems. In line with the current resumption of general interest in neurochemistry there is also an introductory chapter on this subject.

Certain features which appeared gratifying to this reviewer were the inclusion of an up-to-date list of references following each chapter, and the brief section entitled

"Names in Neurology" appearing also at the close of each chapter. These sections present the names of well-known investigators of the nervous system with a brief statement of their accomplishments and may well serve as an introduction to the history of neurology.

This book has apparently been prepared specifically for the medical student and will be most useful to him; but it will also be useful to the trainee in clinical neurology, neurosurgery or psychiatry.

C. V. B.

Colorimetric Analysis. Volume I. Determinations of Clinical and Biochemical Significance. 2nd Ed. By NOEL L. ALLPORT, F.R.I.C., and J. W. KEYSER, M.Sc., Ph.D. (Lond.), A.R.I.C. 424 pages; 23 × 14.5 cm. The Macmillan Company, New York. 1957. Price, $9.00.

The first edition of this work found wide acceptance in England because of the author's critical and practical approach to colorimetric analysis applied to metals, foods, pharmaceutical products and to substances of clinical and biological interest. In order to include more material, the second edition is to be published in two volumes. J. W. Keyser has joined Noel L. Allport in preparing this, the first, volume which includes methods for the determination of substances of clinical and biological interest. The methods, which include many not usually given in laboratory manuals of biological and clinical chemistry, are well presented. Substances which interfere with the reactions, and special precautions are noted in the discussion following each method.

This is a good reference volume for anyone interested in analytical work in the biological fields.

M. A.

Abortion in the United States: Report of a Conference Sponsored by the Planned Parenthood Federation of America, Inc. Edited by MARY STEICHEN CALDERONE, M.D., M.S.P.H. 224 pages; 16 × 24 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1958. Price, $5.50.

Abortion is an absolutely universal phenomenon and is recognized as a major sociomedical problem of our time. With this realization in mind, a unique Arden House Conference dealing with illegal and therapeutic abortion was convened in 1955 under the auspices of the National Committee on Maternal Health. "Abortion in the United States" represents the edited version of the proceedings of that conference.

Forty-three experts from many fields, including a group of eminent gynecologists, present the known data on such topics as illegal abortion in the United States and Scandinavian countries, psychiatric and sociological aspects of the abortion problem, contraception and abortion. An abortionist who "fell into disagreement with the law" candidly reviews his own experiences in the performance of 5,210 such operations. Varying opinions are expressed in a refreshingly frank fashion. The editor is to be commended on retaining the essence, as well as the personality, of all participants' views.

Statistical data dealing with the incidence and extent of the abortion problem are presented by various state and private organizations, including the Institute for Sex Research under the leadership of the late Dr. Alfred C. Kinsey. The limitations

and inaccuracies of this and other statistical material are ably and succinctly stated in this book.

In the final summary of their deliberations, the confreres present a five point program of measures to reduce the high incidence of illegal abortion in the United States. The program, however, does not add any new specific constructive approach that has not already been recognized and applied in a limited fashion.

The appendix of "Abortion in the United States" contains a well edited survey of present abortion and contraception laws in the United States, as well as a brief analysis of the abortion problems in Japan, Germany and the U. S. S. R. Well organized tables are used to clarify complex legal data.

There is something in this book that will be of interest to the gynecologist, the generalist, the psychologist, sociologist and the lawyer.

IRVING KUPERMAN, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Absorption Spectrophotometry. By G. F. LOTHIAN, M.A., F.Inst.P., Lecturer in Physics at the University of Exeter. 246 pages; 22 × 14.5 cm. 1958. The Macmillan Company, New York. Price, $10.75.

Administrative Medicine: Transactions of the Fifth Conference, October 28, 29, and 30, 1956, Princeton, N. J. Edited by GEORGE S. STEVENSON, M.D., National and International Consultant, National Association for Mental Health, New York, N. Y. 197 pages; 23.5 × 15.5 cm. 1958. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.75.

The Author-Publisher-Printer Complex. 3d Ed. By ROBERT S. GILL. 134 pages; 19 × 13 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $2.25.

Bases Physiologiques et Aspects Cliniques de l'Épilepsie. (Actualités Neuro-physiologiques, Semaine Neuro-physiologique de la Salpêtrière.) Publié sous la direction du Pr TH. ALAJOUAININE. 272 pages; 25.5 × 17 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 2.300 fr.

Basic Cardiology. By T. E. GUMPERT, M.B., Ch.B. (Sheff.), F.R.C.P. (Lond.), Physician, Royal Hospital, Sheffield, etc. 168 pages; 22.5 × 14 cm. 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, $6.00.

A Bibliography of Internal Medicine: Communicable Diseases. By ARTHUR L. BLOOMFIELD, M.D. 560 pages; 24 × 16 cm. 1958. The University of Chicago Press, Chicago, Illinois. Price, $10.00.

Chronic Bronchitis, Emphysema and Cor Pulmonale. By C. H. STUART-HARRIS, M.D. (Lond.), F.R.C.P., Sir George Franklin Professor of Medicine of the University of Sheffield; and T. HANLEY, M.D. (Lond.), M.R.C.P., Lecturer in Medicine of the University of Sheffield; written in collaboration with MARJORIE CLIFTON, M.D. (Sheffield), Research Assistant to the M.R.C. Group for Epidemiological Research on Respiratory Diseases; MARGARET M. PLATTS, M.D., B.Sc. (Sheffield), M.R.C.P., J. G. Graves Research Fellow, University of Sheffield; J. D. S. HAMMOND, M.B., Ch.B. (Sheffield), M.R.C.P., Research Assistant and

Tutor in Medicine of the University of Sheffield; and W. WHITAKER, M.D. (Leeds), M.R.C.P., Consultant Cardiologist to the United Leeds Hospitals and the Leeds Regional Hospital Board. 245 pages; 22.5 × 14.0 cm. 1957. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, $8.50.

Diagnostic Anatomy. By WESTON D. GARDNER, M.D., Associate Professor of Anatomy, Marquette University School of Medicine, etc. 376 pages; 25.5 × 17.5 cm. 1958. The C. V. Mosby Company, St. Louis. Price, $10.00.

A Doctor Speaks His Mind. By ROGER I. LEE, M.D. 120 pages; 19.5 × 13.5 cm. 1958. Little, Brown and Company, Boston. Price, $3.00.

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